ORIGINAL

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UNITED STATES DISTRICT COURT

DISTRICT OF NEVADA

Takeda Chemical Industries, Ltd., a foreign corporation; and Takeda Pharmaceuticals, North America, Inc., a Delaware corporation,

Plaintiffs,

vs.

Watson Pharmaceuticals, Inc., a Nevada corporation; Watson Laboratories, Inc., a New York corporation; Watson Pharma, Inc., a Delaware corporation; and Danbury Pharmacal, Inc., a Delaware corporation,

Defendants.

Case No. CV-S-03-1335-LRH-RJJ

COMPLAINT

Plaintiffs Takeda Chemical Industries, Ltd. ("TCI") and Takeda Pharmaceuticals North America, Inc. ("TPNA") (hereafter, collectively, "Takeda") by their undersigned counsel, for their Complaint against defendants Watson Pharmaceuticals, Inc. ("Watson Pharmaceuticals"), Watson Laboratories, Inc. ("Watson Laboratories"), Watson Pharma, Inc. ("Watson Pharma"), and Danbury Pharmacal, Inc. ("Danbury") (collectively, "Watson") allege as follows:

Jurisdiction and Venue

1. This is an action for patent infringement arising under the patent laws of the United States, Title 35, United States Code and arising under 35 U.S.C. §§ 271(e)(2), 271(b), and 281-283. Subject matter jurisdiction is proper under 28 U.S.C. §§ 1331 and 1338(a). Venue is proper under 28 U.S.C. §§ 1391(b)-(c) and 1400(b). Personal jurisdiction over the defendants in Nevada is proper under NRS 14.065, and because defendants are doing business in this jurisdiction.

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Parties

2. TCI is a Japanese corporation having its corporate headquarters in Osaka, Japan and principal place of business in Osaka, Japan. TPNA is a wholly owned U.S. subsidiary of Takeda America Holdings, Inc., which is a wholly owned U.S. subsidiary of TCI. TPNA has its corporate headquarters and principal place of business in Lincolnshire, Illinois and is organized under the laws of Delaware.

3. TCI is engaged in the business of research, developing, manufacturing, and marketing of a broad spectrum of innovative pharmaceutical products, including ACTOS, which comprises the active ingredient pioglitazone.

4. Upon information and belief, Watson Pharmaceuticals which has its corporate headquarters in Corona, California, is incorporated in the State of Nevada and does business in the State of Nevada. Upon information and belief, ANDA No. 76-798 was filed under the name of Watson Pharmaceuticals.

5. Upon information and belief, defendant Watson Laboratories is a wholly owned subsidiary of Watson Pharmaceuticals, subject to Watson's actual control, and is also located in Corona, California. Upon information and belief, Watson Laboratories researches, develops, sells, manufactures and/or distributes pharmaceuticals and is licensed to do business in the State of Nevada and does business in the State of Nevada.

6. Upon information and belief, Watson Pharma is a Delaware corporation with its principal place of business in Morristown, New Jersey. On information and belief, Watson Pharma formerly transacted business under the name Schein Pharmaceuticals, Inc. Upon information and belief, Watson Pharma is a wholly owned subsidiary of Watson Pharmaceuticals, subject to its actual control, and manufactures, markets, sells and/or distributes solid dose pharmaceuticals. Upon information and belief, Watson Pharma is licensed to do business in the State of Nevada and does business in the State of Nevada.

7. Upon information and belief, defendant Danbury is a Delaware corporation with its principal place of business in Carmel, New York. Danbury is a wholly owned subsidiary of

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Watson Pharmaceuticals, subject to its actual control, and manufactures, markets, offers for sale, sells, and/or distributes solid dose pharmaceuticals. Upon information and belief, Danbury does business in the State of Nevada.

8. Upon information and belief, Watson is currently transacting business in the State of Nevada, at least by making and shipping into this Judicial District, or by using, offering to sell or selling or causing others to use, offer to sell or sell, pharmaceutical products. Watson derives substantial revenue from interstate and/or international commerce, including substantial revenue from goods used or consumed or services rendered in the State of Nevada and this Judicial District. By filing its ANDA, Watson has committed, and unless enjoined, will continue to commit a tortious act within the State of Nevada, that Watson expects or should reasonably expect to have consequences within the State of Nevada.

The New Drug Application

9. TPNA sells pioglitazone-containing drug products under the trade name ACTOS® in the United States pursuant to the United States Food and Drug Administration's approval of a New Drug Application ("NDA") held by TPNA (NDA NO. 021073).

10. ACTOS® is approved for use as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes (non-insulin-dependent diabetes mellitus). ACTOS® is indicated for monotherapy. ACTOS® is also indicated for use in combination with a sulfonylurea, metformin, or insulin when diet and exercise plus the single agent does not result in adequate glycemic control.

11. The approval letter for ACTOS®, with approved labeling, was issued by the FDA on July 15, 1999. The approval was for both monotherapy and combination therapy, based upon the FDA's consideration of clinical studies, presented in a single NDA, for both types of therapies.

The Patents in Suit

12. United States Patent No. 5,965,584 ("the '584 patent"), entitled "Pharmaceutical composition," a true and correct copy of which is appended hereto as exhibit A, was duly issued on October 12, 1999 to inventors Hitoshi Ikeda, Takashi Sohda and Hiroyuki Odaka and assigned to plaintiff TCI. The '584 patent claims, *inter alia*, a pharmaceutical composition

comprising a pioglitazone [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]pheny]methyl]-2,4-thiazolidinedione], or salts thereof in combination with a biguanide (e.g., metformin) and methods for treating diabetes which comprise administering a therapeutically effective amount of pioglitazone or salts thereof in combination with a biguanide, such as metformin. Claim 13 recites that pioglitazone and biguanide are administered as an admixture. Claim 14 recites that pioglitazone and biguanide are administered independently.

13. Plaintiff TCI has been and still is the owner, through assignment, of the '584 patent, which expires on June 19, 2016.

14. United States Patent No. 6,329,404 ("the '404 patent"), entitled "Pharmaceutical composition," a true and correct copy of which is appended hereto as Exhibit B, was duly issued on December 11, 2001 to inventors Hitoshi Ikeda, Takashi Sohda and Hiroyuki Odaka, and assigned to plaintiff TCI. The '404 patent claims, *inter alia*, a pharmaceutical composition comprising pioglitazone or salts thereof in combination with an insulin secretion enhancer (e.g., a sulfonylurea, such as glipizide) and methods for treating diabetes which comprise administering a therapeutically effective amount of pioglitazone or salts thereof in combination with an insulin secretion enhancer. Claim 24 recites that the pioglitazone and an insulin secretion enhancer are administered as an admixture. Claim 25 recites that pioglitazone and an insulin secretion enhancer are administered independently.

15. Plaintiff TCI has been and still is the owner through assignment of the '404 patent, which expires on June 19, 2016.

16. United States Patent No. 6,140,383 ("the '383 patent"), entitled "Pharmaceutical composition," a true and correct copy of which is appended hereto as exhibit C, was duly issued on November 21, 2000 to inventors Hitoshi Ikeda, Takashi Sohda and Hiroyuki Odaka, and assigned to plaintiff TCI. The '383 patent claims, *inter alia*, methods for treating a glycometabolism disorder which comprise administering pioglitazone or salts thereof in combination with an insulin secretion enhancer (e.g., a sulfonylurea).

17. Plaintiff TCI has been and still is the owner through assignment of the '383 patent, which expires on June 19, 2016.

18. United States Patent No. 6,166,042 ("the '042 patent"), entitled "Pharmaceutical

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composition," a true and correct copy of which is appended hereto as exhibit D, was duly issued on December 26, 2000 to inventors Hitoshi Ikeda, Takashi Sohda and Hiroyuki Odaka, and assigned to plaintiff TCI. The '042 patent claims, *inter alia*, methods for treating a glycometabolism disorder which comprise administering pioglitazone or salts thereof in combination with a biguanide, e.g., metformin.

19. Plaintiff TCI has been and still is the owner through assignment of the '042 patent, which expires on June 19, 2016.

20. United States Patent No. 6,166,043 ("the '043 patent"), entitled "Pharmaceutical composition," a true and correct copy of which is appended hereto as exhibit E, was duly issued on December 26, 2000 to inventors Hitoshi Ikeda, Takashi Sohda and Hiroyuki Odaka, and assigned to plaintiff TCI. The '043 patent claims, *inter alia*, methods for reducing the amount of active components administered to a diabetic patent, which comprise administering a therapeutically effective amount of pioglitazone or salts thereof in combination with biguanide, e.g., metformin.

21. Plaintiff TCI has been and still is the owner through assignment of the '043 patent, which expires on June 19, 2016.

22. United States Patent No. 6,172,090 ("the 090 patent"), entitled "Pharmaceutical composition," a true and correct copy of which is appended hereto as exhibit F, was duly issued on January 9, 2001 to inventors Hitoshi Ikeda, Takashi Sohda and Hiroyuki Odaka, and assigned to plaintiff TCI. The '090 patent claims, *inter alia*, methods for reducing the side effects of active components administered to a diabetic patient, which comprise administering a therapeutically effective amount of pioglitazone or salts thereof in combination with a biguanide, e.g., metformin, as the active components.

23. Plaintiff TCI has been and still is the owner through assignment of the '090 patent, which expires on June 19, 2016.

24. United States Patent No. 6,211,205 ("the '205 patent"), entitled "Pharmaceutical composition," a true and correct copy of which is appended hereto as exhibit G, was duly issued on April 3, 2001 to investors Hitoshi Ikeda, Takashi Sohda and Hiroyuki Odaka, and assigned to plaintiff TCI. The '205 patent claims, *inter alia*, methods for reducing the amount

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of active components administered to a diabetic patient, which comprises administering a therapeutically effective amount of pioglitazone or salts thereof in combination with an insulin secretion enhancer (e.g., a sulfonylurea).

25. Plaintiff TCI has been and still is the owner through assignment of the '205 patent, which expires on June 19, 2016.

26. United States Patent No. 6,271,243 ("the 243 patent"), entitled "Pharmaceutical composition," a true and correct copy of which is appended hereto as exhibit H, was duly issued on August 7, 2001 to inventors Hitoshi Ikeda, Takashi Sohda and Hiroyuki Odaka, and assigned to plaintiff TCI. The '243 patent claims, *inter alia*, methods for reducing the side effects of active components administered to a diabetic patient, which comprises administering a therapeutically effective amount of pioglitazone or salts thereof in combination with an insulin preparation.

27. Plaintiff TCI has been and still is the owner through assignment of the '243 patent, which expires on June 19, 2016.

28. United States Patent No. 6,303,640 ("the '640 patent"), entitled "Pharmaceutical composition," a true and correct copy of which is appended hereto as exhibit I, was duly issued on October 16, 2001 to inventors Hitoshi Ikeda, Takashi Sohda and Hiroyuki Odaka, and assigned to plaintiff TCI. The '640 patent claims, *inter alia*, methods for reducing the side effects of active components administered to a diabetic patient, which comprises administering a therapeutically effective amount of pioglitazone or salt thereof in combination with an insulin secretion enhancer (e.g., a sulfonylurea).

29. Plaintiff TCI has been and still is the owner through assignment of the '640 patent, which expires on August 9, 2016.

30. Plaintiff TCI has granted an exclusive license to plaintiff TPNA under the '584 patent, the '404 patent, the '383 patent, the '042 patent, the '043 patent, the '090 patent, the '205 patent, the 243 patent, and the '640 patent (collectively, "Takeda Patents").

31. In accordance with its exclusive license, plaintiff TPNA sells pioglitazone-containing drug products under the trade name ACTOS® in the United States. Sales of TPNA's pioglitazone-containing drug products are made pursuant to approval by the FDA of

NDA NO. 021073.

32. Plaintiff TCI manufactures the pioglitazone-containing drug products sold by TPNA.

33. Plaintiffs TCI and TPNA will be both substantially and irreparably harmed by infringement of any of the Takeda Patents. There is no adequate remedy at law.

COUNT I
(INDUCEMENT OF INFRINGEMENT OF U.S.PATENT NO. 5,965,584 UNDER 35 U.S.C. § 271(e)(2)(A) BY DEFENDANTS)

34. Plaintiffs TCI and TPNA repeat and incorporate herein by reference the allegations contained in paragraphs 1 through 33 above.

35. Upon information and belief, defendant Watson Pharmaceuticals, filed an Abbreviated New Drug Application ("ANDA") with the Food and Drug Administration ("FDA") under 21 U.S.C. § 355(j) (ANDA No. 76-798) seeking approval to market 15 mg, 30 mg, and 45 mg tablets comprising pioglitazone as its HCI salt.

36. By this ANDA filing, Watson has indicated that it intends to engage, and that there is substantial likelihood that it will engage in the commercial manufacture, use, offer for sale and/or sale of plaintiffs' patented pioglitazone drug products immediately or imminently upon receiving FDA approval to do so. Also by its ANDA filing, Watson has indicated that its drug products containing pioglitazone are bioequivalent to Takeda's pioglitaznoe drug products.

37. By its ANDA filing, Watson seeks to obtain approval to commercially manufacture, use, offer for sale and/or sell alleged generic equivalents of plaintiffs' ACTOS® pioglitazone drug products prior to the expiration date of the '584 patent.

38. By a letter ("The Letter") dated September 9, 2003, Watson informed plaintiffs that Watson had filed a certification to the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV). A true and correct copy of The Letter is attached as exhibit J. On or about September 12, 2003, NDA holder, TPNA, received The Letter. On or about September 22, 2003, patent owner, TCI, received a duplicate original of The Letter.

39. The Letter, purporting to be Watson's Notice of Certification under 21 U.S.C.§ 355(j)(2)(B)(ii), indicates that Watson intends to manufacture, use, offer for sale, and/or sell,

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pioglitazone as its HCI salt prior to the expiration of the '584 patent. The Letter alleges that in Watson's opinion, its manufacture, use, offer for sale and/or sale of pioglitazone in the United States during the unexpired term of the '584 patent will not infringe any valid claim of the '584 patent because Watson will be offering for sale a pioglitazone product which will be labeled for use in monotherapy.

40. Watson's filing of ANDA No. 76-798 for the purpose of obtaining FDA approval to engage in the commercial manufacture, use, offer for sale and/or sale, or inducement thereof, drug products containing pioglitazone or salts thereof before the expiration of the '584 patent is an act of infringement under 35 U.S.C. § 271(e)(2)(A).

41. Upon information and belief, Watson's manufacture, use, offer for sale, and/or sale of its proposed pioglitazone drug product will induce infringement of at least one claim of the '584 patent under 35 U.S.C. § 271(e)(2)(A).

42. Upon information and belief, Watson is aware or reasonably should be aware, of the widespread use of pioglitazone in combination therapy, and that such use does not require a physician to co-prescribe pioglitazone with a biguanide, e.g., metformin. Further, patients routinely take pioglitazone in combination with additional active components, such as biguanides, e.g., metformin. The intended use of pioglitazone in combination therapy to treat diabetes would be readily apparent to a customer of Watson (e.g., including, without limitation, a physician, a pharmacist, a pharmacy benefits management company, health care provider who establishes drug formularies for its insurers and/or a patient).

43. Upon information and belief, Watson currently manufactures, markets, offers for sale, and/or sells the biguanide, metformin.

44. Upon information and belief, Watson's proposed label for its pioglitazone drug products does not restrict the use of those products to only monotherapy. As is well known to Watson and its customers, the majority of patents treated with pioglitazone take it in combination with another antidiabetic drug, namely, such patients obtain treatment with pioglitazone in combination with a biguanide such as metformin, treatment with pioglitazone in combination with an insulin secretion enhancer such as a sulfonylurea, and/or treatment with pioglitazone in combination with an insulin preparation. The beneficial effects of such

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combination therapy are well known to Watson and customers of Watson. On information and belief, Watson will be marketing pioglitazone with specific intent, and/or with the desire to actively induce, aid and abet infringement of the '584 patent. Watson knows or reasonably should know that its proposed conduct will induce infringement.

45. Upon information and belief, Watson's generic marketing practices include listing generic products on its website and referring consumers to a corresponding brand name product. Upon information and belief, Watson intends to do the same for any approved generic pioglitazone, namely, Watson intends to list its generic product and refer consumers to Takeda's product, ACTOS®. Upon information and belief, such marketing practices are substantially likely to lead a consumer of generic pioglitazone to infer that prescribing information for ACTOS®, which includes directions relating to the use of combinations of ACTOS® and metformin, a biguanide, also applies to Watson's generic pioglitazone-containing drug product.

46. Upon information and belief, Watson has planned and intended to actively induce others to infringe the '584 patent when its ANDA application is approved and plans and intends to do so on approval.

47. Upon information and belief, the acts of infringement alleged above are and have been deliberate and willful, and in full knowledge of the existence of the '584 patent.

48. Unless Watson is enjoined from infringing and inducing the infringement of the '584 patent, plaintiffs will suffer substantial and irreparable injury. Plaintiffs have no adequate remedy at law.

COUNT II
(INDUCEMENT OF INFRINGEMENT OF U.S. PATENT NO. 6,329,404 UNDER 35 U.S.C. § 271(e)(2)(A) BY DEFENDANTS)

49. Plaintiffs TCI and TPNA repeat and incorporate herein by reference the allegations contained in paragraphs 1 through 48 above.

50. Watson' Letter, purporting to be Watson's Notice of Certification under 21 U.S.C. § 355(j)(2)(B)(ii), also indicates that Watson intends to manufacture, use, sell, or offer for sale, pioglitazone as its HCl salt prior to the expiration of the '404 patent. The Letter alleges that in Watson's opinion, its manufacture, use, offer for sale, and/or offer for sale in the

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United States during the unexpired term of the '404 patent will not infringe any valid claim of the '404 patent because Watson will be offering for sale a pioglitazone product which will be labeled for use in monotherapy.

51. Watson's manufacture, use, offer for sale, and/or sale of its proposed pioglitazone drug product will induce infringement of at least one claim of the '404 patent under 35 U.S.C. § 271(e)(2)(A).

52. Upon information and belief, Watson is aware or reasonably should be aware, of the widespread use of pioglitazone in combination therapy to treat diabetes, and that such use does not require a physician to co-prescribe pioglitazone with an insulin secretion enhancer (e.g., a sulfonylurea). Further, patients routinely take pioglitazone in combination with additional active components, such as insulin secretion enhancers. The intended use of pioglitazone in combination therapy to treat diabetes would be readily apparent to a customer of Watson (e.g., including, without limitation, a physician, pharmacist, pharmacy benefits management company, health care provider who establishes drug formularies for its insurers and/or patient).

53. Upon information and belief, Watson currently manufactures, markets, offers for sale, and/or sells the insulin secretion enhancer, glipizide.

54. Upon information and belief, Watson's proposed label for its pioglitazone drug products does not restrict the use of those products to only monotherapy. As is well known to Watson and its customers, the majority of patients treated with pioglitazone take it in combination with another antidiabetic drug, namely, such patients obtain treatment with pioglitazone in combination with a biguanide such as metformin, in combination with an insulin secretion enhancer such as a sulfonylurea, and/or in combination with an insulin preparation. The beneficial effects of such co-administration and/or interactions are well known to Watson and customers of Watson. On information and belief, Watson will be marketing pioglitazone with specific intent, and/or with the desire to actively induce, aid and abet infringement of the '404 patent. Watson knows or reasonably should know that its proposed conduct will induce infringement.

55. Upon information and belief, Watson's generic marketing practices include

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listing generic products on its website and referring consumers to a corresponding brand name product. Upon information and belief, Watson intends to do the same for any approved generic pioglitazone, namely, Watson intends to list its generic product and to refer consumers to Takeda's product, ACTOS®. Upon information and belief, such marketing practices are substantially likely to lead a consumer of generic pioglitazone to infer that prescribing information for ACTOS®, which includes directions relating to the use of combinations of ACTOS® and an insulin secretion enhancer (e.g., a sulfonylurea), also applies to Watson's generic pioglitazone-containing drug product.

56. Upon information and belief, Watson has planned and intended to actively induce others to infringe the '404 patent when its ANDA application is approved and plans and intends to do so on approval.

57. Upon information and belief, the acts of infringement alleged above are and have been deliberate and willful, and in full knowledge of the existence of the '404 patent.

58. Unless Watson is enjoined from infringing and inducing the infringement of the '404 patent, plaintiffs will suffer substantial and irreparable injury. Plaintiffs have no adequate remedy at law.

COUNT III
(INFRINGEMENT OF METHOD CLAIMS OF THE '584 PATENT UNDER 35 U.S.C. § 271(b))

59. Plaintiffs TCI and TPNA repeat and incorporate herein by reference the allegations contained in paragraphs 1 through 58 above.

60. On information and belief, approval of ANDA 76-798 is substantially likely to result in the commercial use, manufacture, offer for sale, and/or sale, or inducement thereof, of a drug product which is marketed and sold for use in a method claimed in one or more claims of the '584 patent, immediately or imminently upon approval of the ANDA.

61. Upon information and belief, Watson is aware or reasonably should be aware, of the widespread use of pioglitazone in the methods of one or more claims of the '584 patent and that use in such methods does not require a physician to co-prescribe pioglitazone with a biguanide, e.g., metformin. Further, patients routinely take pioglitazone in combination with additional active components, such as biguanides for use in methods covered by the '584

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patent. The intended use of pioglitazone in combination therapy to treat diabetes would be readily apparent to a customer of Watson.

62. Upon information and belief, Watson's proposed label for its pioglitazone drug products does not restrict the use of those products to only monotherapy. As is well known to Watson and its customers, the majority of patients treated with pioglitazone take it in combination with another antidiabetic drug, namely, such patients obtain treatment with pioglitazone in combination with a biguanide such as metformin, in combination with an insulin secretion enhancer such as a sulfonylurea, and/or in combination with an insulin preparation. The beneficial effects of such co-administration and/or interactions are well known to Watson and customers of Watson. On information and belief, Watson will be marketing pioglitazone with specific intent, and/or with the desire to actively induce, aid and abet infringement of the '584 patent. Watson knows or reasonably should know that its proposed conduct will induce infringement.

63. Upon information and belief, Watson's generic marketing practices include listing generic products on its website and referring consumers to a corresponding brand name product. Upon information and belief, Watson intends to do the same for any approved generic pioglitazone, namely, Watson intends to list its generic product and refer consumers to Takeda's product ACTOS®. Upon information and belief, such marketing practices are substantially likely to lead a consumer of generic pioglitazone to infer that prescribing information for ACTOS®, which includes directions relating to the use of combinations of ACTOS® and a biguanide, also applies to Watson's generic pioglitazone-containing drug product.

64. Upon information and belief, the acts of infringement alleged above are and have been deliberate and willful.

65. Plaintiffs will be substantially and irreparably harmed if defendants are not enjoined from inducing the infringement of the '584 patent. Plaintiffs have no adequate remedy at law.

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COUNT IV
(INFRINGEMENT OF METHOD CLAIMS OF THE '404 PATENT UNDER 35 U.S.C. § 271(b))

66. Plaintiffs TCI and TPNA repeat and incorporate herein by reference the allegations contained in paragraphs 1 through 65 above.

67. On information and belief, approval of ANDA 76-798 is substantially likely to result in the commercial use, manufacture, offer for sale, and/or sale, or inducement thereof, of a drug product which is marketed and sold for use in a methods claimed in one or more claims of the '404 patent, immediately or imminently upon approval of the ANDA.

68. Upon information and belief, Watson is aware or reasonably should be aware, of the widespread use of pioglitazone in the methods of one or more claims of the '404 patent and that use in such methods does not require a physician to co-prescribe pioglitazone with an insulin secretion enhancer (e.g., a sulfonylurea). Further, patients routinely take pioglitazone in combination with additional active components, such as insulin secretion enhancers for use in methods covered by the '404 patent. The intended use of pioglitazone in combination therapy to treat diabetes would be readily apparent to a customer of Watson.

69. Upon information and belief, Watson's proposed label for its pioglitazone drug products does not restrict the use of those products to only monotherapy. As is well known to Watson and its customers, the majority of patients treated with pioglitazone take it in combination with another antidiabetic drug, namely, such patients obtain treatment with pioglitazone in combination with a biguanide such as metformin, in combination with an insulin secretion enhancer such as a sulfonylurea, and/or in combination with an insulin preparation. The beneficial effects of such co-administration and/or interactions are well known to Watson and customers of Watson. On information and belief, Watson will be marketing pioglitazone with specific intent, and/or with the desire to actively induce, aid and abet infringement of the '404 patent. Watson knows or reasonably should know that its proposed conduct will induce infringement.

70. Upon information and belief, Watson's generic marketing practices include listing generic products on its website and referring consumers to a corresponding brand name product. Upon information and belief, Watson intends to do the same for any approved generic

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pioglitazone, namely, Watson intends to list its generic product and refer consumers to compare the generic product with ACTOS®. Upon information and belief, such marketing practices are substantially likely to lead a consumer of generic pioglitazone to infer that prescribing information for ACTOS®, which includes directions relating to the use of combinations of ACTOS® and an insulin secretion enhancer (e.g., a sulfonylurea), also applies to Watson's generic pioglitazone-containing drug product.

71. Upon information and belief, the acts of infringement alleged above are and have been deliberate and willful.

72. Plaintiffs will be substantially and irreparably harmed if defendants are not enjoined from inducing the infringement of the '404 patent. Plaintiffs have no adequate remedy at law.

COUNT V
INFRINGEMENT OF THE '383 PATENT UNDER 35 U.S.C. § 271(b))

73. Plaintiffs TCI and TPNA repeat and incorporate herein by reference the allegations contained in paragraphs 1 through 72 above.

74. On information and belief, approval of ANDA 76-798 is substantially likely to result in the commercial use, manufacture, offer for sale, and/or sale of a drug product which is marketed and sold for use in a methods claimed in one or more claims of the '383 patent, immediately or imminently upon approval of the ANDA.

75. Upon information and belief, Watson is aware or reasonably should be aware, of the widespread use of pioglitazone in the methods of one or more claims of the '383 patent and that use in such methods does not require a physician to co-prescribe pioglitazone with an insulin secretion enhancer (e.g., a sulfonylurea). Further, patients routinely take pioglitazone in combination with additional active components, such as insulin secretion enhancers for use in methods covered by the '383 patent. The intended use of pioglitazone in combination therapy to treat a glycometabolism disorder, such as diabetes, would be readily apparent to a customer of Watson.

76. Upon information and belief, Watson's proposed label for its pioglitazone drug products does not restrict the use of those products to only monotherapy. As is well known to Watson and its customers, the majority of patients treated with pioglitazone take it in

combination with another antidiabetic drug, namely, such patients obtain treatment with pioglitazone in combination with a biguanide such as metformin, in combination with an insulin secretion enhancer such as a sulfonylurea, and/or in combination with an insulin preparation. The beneficial effects of such co-administration and/or interactions are well known to Watson and customers of Watson. On information and belief, Watson will be marketing pioglitazone with specific intent, and/or with the desire to actively induce, aid and abet infringement of the '383 patent. Watson knows or reasonably should know that its proposed conduct will induce infringement.

77. Upon information and belief, Watson's generic marketing practices include listing generic products on its website and referring consumers to a corresponding brand name product. Upon information and belief, Watson intends to do the same for any approved generic pioglitazone, namely, Watson intends to list its generic Takeda's product, ACTOS®. Upon information and belief, such marketing practices are substantially likely to lead a consumer of generic pioglitazone to infer that prescribing information for ACTOS®, which includes directions relating to the use of combinations of ACTOS® and an insulin secretion enhancer (e.g., a sulfonylurea), also applies to Watson's generic pioglitazone-containing drug product.

78. Upon information and belief, the acts of infringement alleged above are and have been deliberate and willful.

79. Plaintiffs will be substantially and irreparably harmed if defendants are not enjoined from inducing the infringement of the '383 patent. Plaintiffs have no adequate remedy at law.

COUNT VI
(INFRINGEMENT OF THE '042 PATENT UNDER 35 U.S.C. § 271(b))

80. Plaintiffs TCI and TPNA repeat and incorporate herein by reference the allegations contained in paragraphs 1 through 79 above.

81. On information and belief, approval of ANDA 76-798 is substantially likely to result in the commercial use, manufacture, offer for sale, and/or sale, or inducement thereof, of a drug product which is marketed and sold for use in a methods claimed in one or more claims of the '042 patent, immediately or imminently upon approval of the ANDA.

82. Upon information and belief, Watson is aware or reasonably should be aware, of

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the widespread use of pioglitazone in the methods of one or more claims of the '042 patent and that use in such methods does not require a physician to co-prescribe pioglitazone with biguanide, e.g., metformin. Further, patients routinely take pioglitazone in combination with additional active components, such as biguanides for use in methods covered by the '042 patent. The intended use of pioglitazone in combination therapy to treat a glycometabolism disorder, such as diabetes, would be readily apparent to a customer of Watson.

83. Upon information and belief, Watson's proposed label for its pioglitazone drug products does not restrict the use of those products to only monotherapy. As is well known to Watson and its customers, the majority of patients treated with pioglitazone take it in combination with another antidiabetic drug, namely, such patients obtain treatment with pioglitazone in combination with a biguanide such as metformin, in combination with an insulin secretion enhancer such as a sulfonylurea, and/or in combination with an insulin preparation. The beneficial effects of such co-administration and/or interactions are well known to Watson and customers of Watson. Upon information and belief, Watson will be marketing pioglitazone with specific intent, and/or with the desire to actively induce, aid and abet infringement of the '042 patent. Watson knows or reasonably should know that its proposed conduct will induce infringement.

84. Upon information and belief, Watson's generic marketing practices include listing generic products on its website and referring consumers to a corresponding brand name product. Upon information and belief, Watson intends to do the same for any approved generic pioglitazone, namely, Watson intends to list its generic product and refer consumers to Takeda's product, ACTOS®. On information and belief, such marketing practices are substantially likely to lead a consumer of generic pioglitazone to infer that prescribing information for ACTOS®, which includes directions relating to the use of combinations of ACTOS® and a biguanide, e.g., metformin, also applies to Watson's generic pioglitazone-containing drug product.

85. Upon information and belief, the acts of infringement alleged above are and have been deliberate and willful.

86. Plaintiffs will be substantially and irreparably harmed if defendants are not

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enjoined from inducing the infringement of the '042 patent. Plaintiffs have no adequate remedy at law.

COUNT VII
(INFRINGEMENT OF THE '043 PATENT UNDER 35 U.S.C. § 271(b))

87. Plaintiffs TCI and TPNA repeat and incorporate herein by reference the allegations contained in paragraphs 1 through 86 above.

88. On information and belief, approval of ANDA 76-798 is substantially likely to result in the commercial use, manufacture, offer for sale, and/or sale, or inducement thereof, of a drug product which is marketed and sold for use in a methods claimed in one or more claims of the '043 patent, immediately or imminently upon approval of the ANDA.

89. Upon information and belief, Watson is aware or reasonably should be aware, of the widespread use of pioglitazone in the methods of one or more claims of the '043 patents and that use in such methods does not require a physician to co-prescribe pioglitazone with a biguanide, e.g., metformin. Further, patients routinely take pioglitazone in combination with additional active components, such as biguanides for use in methods covered by the '043 patent. The intended use of pioglitazone in combination therapy to reduce the amount of active components used in such therapy would be readily apparent to a customer of Watson.

90. Upon information and belief, Watson's proposed label for its pioglitazone drug products does not restrict the use of those products to only monotherapy. As is well known to Watson and its customers, the majority of patients treated with pioglitazone take it in combination with another antidiabetic drug, namely, such patients obtain treatment with pioglitazone in combination with a biguanide such as metformin, in combination with an insulin secretion enhancer such as a sulfonylurea, and/or in combination with an insulin preparation. The beneficial effects of such co-administration and/or interactions are well known to Watson and customers of Watson. On information and belief, Watson will be marketing pioglitazone with specific intent, and/or with the desire to actively induce, aid and abet infringement of the '043 patent. Watson knows or reasonably should know that its proposed conduct will induce infringement.

91. Upon information and belief, Watson's generic marketing practices include listing generic products on its website and referring consumers to a corresponding brand name

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product. Upon information and belief, Watson intends to do the same for any approved generic pioglitazone, namely, Watson intends to list its generic product and refer consumers to Takeda's product, ACTOS®. Upon information and belief, such marketing practices are substantially likely to lead a consumer of generic pioglitazone to infer that prescribing information for ACTOS®, which includes directions relating to the use of combinations of ACTOS® and a biguanide, e.g., metformin, also applies to Watson's generic pioglitazone-containing drug product.

92. Upon information and belief, the acts of infringement alleged above are and have been deliberate and willful.

93. Plaintiffs will be substantially and irreparably harmed if defendants are not enjoined from inducing the infringement of the '043 patent. Plaintiffs have no adequate remedy at law.

COUNT VIII
(INFRINGEMENT OF THE '090 PATENT UNDER 35 U.S.C. § 271(b))

94. Plaintiffs TCI and TPNA repeat and incorporate herein by reference the allegations contained in paragraphs 1 through 93 above.

95. On information and belief, approval of ANDA 76-798 is substantially likely to result in the commercial use, manufacture, offer for sale, and/or sale, or importation thereof, of a drug product which is marketed and sold for use in a methods claimed in one or more claims of the '090 patent, immediately or imminently upon approval of the ANDA.

96. Upon information and belief, Watson is aware or reasonably should be aware, of the widespread use of pioglitazone in the methods of one or more claims of the '090 patent and that use in such methods does not require a physician to co-prescribe pioglitazone with a biguanide. Further, patients routinely take pioglitazone in combination with additional active components, such as biguanides, e.g., metformin, for use in methods covered by the '090 patent. The intended use of pioglitazone in combination therapy to reduce side effects of such therapy would be readily apparent to a customer of Watson.

97. Upon information and belief, Watson's proposed label for its pioglitazone drug products does not restrict the use of those products to only monotherapy. As is well known to Watson and its customers, the majority of patients treated with pioglitazone take it in

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combination with another antidiabetic drug, namely, such patients obtain treatment with pioglitazone in combination with a biguanide such as metformin, in combination with an insulin secretion enhancer such as a sulfonylurea, and/or in combination with an insulin preparation. The beneficial effects of such co-administration and/or interactions are well known to Watson and customers of Watson. Upon information and belief, Watson will be marketing pioglitazone with specific intent, and/or with the desire to actively induce, aid and abet infringement of the '090 patent. Watson knows or reasonably should know that its proposed conduct will induce infringement.

98. Upon information and belief, Watson's generic marketing practices include listing generic products on its website and referring consumers to a corresponding brand name product. Upon information and belief, Watson intends to do the same for any approved generic pioglitazone, namely, Watson intends to list its generic product and refer consumers to Takeda's product, ACTOS®. Upon information and belief, such marketing practices are substantially likely to lead a consumer of generic pioglitazone to infer that prescribing information for ACTOS®, which includes directions relating to the use of combinations of ACTOS® and a biguanide, e.g., metformin, also applies to Watson's generic pioglitazone-containing drug product.

99. Upon information and belief, the acts of infringement alleged above are and have been deliberate and willful.

100. Plaintiffs will be substantially and irreparably harmed if defendants are not enjoined from inducing the infringement of the '090 patent. Plaintiffs have no adequate remedy at law.

COUNT IX
(INFRINGEMENT OF THE '205 PATENT UNDER 35 U.S.C. § 271(b))

101. Plaintiffs TCI and TPNA repeat and incorporate herein by reference the allegations contained in paragraphs 1 through 100 above.

102. On information and belief, approval of ANDA 76-798 is substantially likely to result in the commercial use, manufacture, offer for sale, and/or sale, or importation thereof, of a drug product which is marketed and sold for use in a methods claimed in one or more claims of the '205 patent, immediately or imminently upon approval of the ANDA.

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103. Upon information and belief, Watson is aware or reasonably should be aware, of the widespread use of pioglitazone in the methods of one or more claims of the '205 patent and that use in such methods does not require a physician to co-prescribe pioglitazone with an insulin secretion enhancer (e.g., a sulfonylurea). Further, patients routinely take pioglitazone in combination with additional active components, such as insulin secretion enhancers for use in methods covered by the '205 patent. The intended use of pioglitazone in combination therapy to reduce the amount of active components used in such therapy would be readily apparent to a customer of Watson.

104. Upon information and belief, Watson's proposed label for its pioglitazone drug products does not restrict the use of those products to only monotherapy. As is well known to Watson and its customers, the majority of patients treated with pioglitazone take it in combination with another antidiabetic drug, namely, such patients obtain treatment with pioglitazone in combination with a biguanide such as metformin, in combination with an insulin secretion enhancer such as a sulfonylurea, and/or in combination with an insulin preparation. The beneficial effects of such co-administration and/or interactions are well known to Watson and customers of Watson. On information and belief, Watson will be marketing pioglitazone with specific intent, and/or with the desire to actively induce, aid and abet infringement of the '205 patent. Watson knows or reasonably should know that its proposed conduct will induce infringement.

105. Upon information and belief, Watson's generic marketing practices include listing generic products on its website and referring consumers to a corresponding brand name product. Upon information and belief, Watson intends to do the same for any approved generic pioglitazone, namely, Watson intends to list its generic product and refer consumers to Takeda's product, ACTOS®. Upon information and belief, such marketing practices are substantially likely to lead a consumer of generic pioglitazone to infer that prescribing information for ACTOS®, which includes directions relating to the use of combinations of ACTOS® and an insulin secretion enhancer (e.g., a sulfonylurea), also applies to Watson's generic pioglitazone-containing drug product.

106. Upon information and belief, the acts of infringement alleged above are and have been deliberate and willful.

107. Plaintiffs will be substantially and irreparably harmed if defendants are not enjoined from inducing the infringement of the '205 patent. Plaintiffs have no adequate remedy at law.

COUNT X
(INFRINGEMENT OF THE '243 PATENT UNDER 35 U.S.C. § 271(b))

118. Plaintiffs TCI and TPNA repeat and incorporate herein by reference the allegations contained in paragraphs 1 through 107 above.

119. On information and belief, approval of ANDA 76-798 is substantially likely toresult in the commercial use, manufacture, offer for sale, and/or sale, or inducement thereof, of a drug product which is marketed and sold for use in a methods claimed in one or more claims of the '243 patent, immediately or imminently upon approval of the ANDA.

120. Upon information and belief, Watson is aware or reasonably should be aware, of the widespread use of pioglitazone in the methods of one or more claims of the '243 patents and that use in such methods does not require a physician to co-prescribe pioglitazone with an insulin preparation. Further, patients routinely take pioglitazone in combination with additional active components, such as insulin preparations for use in methods covered by the '243 patent. The intended use of pioglitazone in combination therapy to treat a diabetic patient to reduce side effects of active components used in such therapy would be readily apparent to a customer of Watson.

121. On information and belief, Watson's proposed label for its pioglitazone drug products does not restrict the use of those products to only monotherapy. As is well known to Watson and its customers, the majority of patients treated with pioglitazone take it in combination with another antidiabetic drug, namely, such patients obtain treatment with pioglitazone in combination with a biguanide such as metformin, in combination with an insulin secretion enhancer such as a sulfonylurea, and/or in combination with an insulin preparation. The beneficial effects of such co-administration and/or interactions are well known to Watson and customers of Watson. On information and belief, Watson will be marketing pioglitazone with specific intent, and/or with the desire to actively induce, aid and

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abet infringement of the '243 patent. Watson knows or reasonably should know that its proposed conduct will induce infringement.

122. Upon information and belief, Watson's generic marketing practices include listing generic products on its website and referring consumers to corresponding brand name product. Upon information and belief, Watson intends to do the same for any approved generic pioglitazone, namely, Watson intends to list its generic Takeda's product, ACTOS®. Upon information and belief, such marketing practices are substantially likely to lead a consumer of generic pioglitazone to infer that prescribing information for ACTOS®, which includes directions relating to the use of combinations of ACTOS® and an insulin preparation, also applies to Watson's generic pioglitazone-containing drug product.

123. Upon information and belief, the acts of infringement alleged above are and have been deliberate and willful, for which plaintiffs are entitled to an award of punitive damages to punish defendant's, and each of them, and to make an example of them to deter them and others from engaging in similar, future behavior.

124. Plaintiffs will be substantially and irreparably harmed if defendants are not enjoined from inducing the infringement of the '243 patent. Plaintiffs have no adequate remedy at law.

COUNT XI
(INFRINGEMENT OF THE '640 PATENT UNDER 35 U.S.C. § 271(b))

125. Plaintiffs TCI and TPNA repeat and incorporate herein by reference the allegations contained in paragraphs 1 through 124 above.

126. On information and belief, approval of ANDA 76-798 is substantially likely to result in the commercial use, manufacture, offer for sale, and/or sale, or importation thereof, of a drug product which is marketed and sold for use in a methods claimed in one or more claims of the '640 patent, immediately or imminently upon approval of the ANDA.

127. Upon information and belief, Watson is aware or reasonably should be aware, of the widespread use of pioglitazone in the methods of one or more claims of the '640 patents and that use in such methods does not require a physician to co-prescribe pioglitazone with an insulin secretion enhancer (e.g., sulfonylurea). Further, patients routinely take pioglitazone in combination with additional active components, such as insulin secretion enhancers for use in

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methods covered by the '640 patent. The intended use of pioglitazone in combination therapy and to reduce side effects of active components used in such therapy would be readily apparent to a customer of Watson.

128. Upon information and belief, Watson's proposed label for its pioglitazone drug products does not restrict the use of those products to only monotherapy. As is well known to Watson and its customers, the majority of patients treated with pioglitazone take it in combination with another antidiabetic drug, namely, such patients obtain treatment with pioglitazone in combination with a biguanide such as metformin, in combination with an insulin secretion enhancer such as a sulfonylurea, and/or in combination with an insulin preparation. The beneficial effects of such co-administration and/or interactions are well known to Watson and customers of Watson. On information and belief, Watson will be marketing pioglitazone with specific intent, and/or with the desire to actively induce, aid and abet infringement of the '640 patent. Watson knows or reasonably should know that its proposed conduct will induce infringement.

129. Upon information and belief, Watson's generic marketing practices include listing generic products on its website and referring consumers to a corresponding brand name product. Upon information and belief, Watson intends to do the same for any approved generic pioglitazone, namely, Watson intends to list its generic product and refer consumers to Takeda's product, ACTOS®. Upon information and belief, such marketing practices are substantially likely to lead a consumer of generic pioglitazone to infer that prescribing information for ACTOS®, which includes directions relating to the use of combinations of ACTOS® and an insulin secretion enhancer (e.g., a sulfonylurea), also applies to Watson's generic pioglitazone-containing drug product.

130. Upon information and belief, the acts of infringement alleged above are and have been deliberate and willful.

131. Plaintiffs will be substantially and irreparably harmed if defendants are not enjoined from inducing the infringement of the '640 patent.

WHEREFORE, Plaintiffs request the following relief:

(a) a judgment that making, using, selling, offering to sell and/or importing Watson's drug product for which it seeks FDA approval or its active ingredient pioglitazone, and/or inducing the same, will infringe at least one claim of the Takeda Patents;

(b) a judgment that inducing the making, using, offering for sale, selling and/or importing of Watson's drug product or its active ingredient pioglitazone, and/or inducing the same, will infringe at least one claim of one or more of the Takeda Patents;

(c) a judgment and order pursuant to 35 U.S.C. § 271(e)(4)(A) providing that the effective date of any FDA approval for Watson to commercially to make, use, sell, offer to sell or import pioglitazone or any drug product containing pioglitazone be no earlier than the date following the expiration date of the last to expire of the '584 patent or the '404 patent;

(d) a permanent injunction restraining and enjoining against any infringement by defendants, their officers, agents, attorneys, and/or employees and those acting in privity or concert with it, of the Takeda Patents through the commercial manufacture, use, sale, offer for sale or importation into the United States of pioglitazone or any drug product containing pioglitazone, and/or any inducement of the same;

(e) Attorneys' fees in this action under 35 U.S.C. § 285;

(f) Such further and other relief as this Court may deem just and proper.

Dated this 23rd day of October, 2003.

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US005965584A

United States Patent [19]

Ikeda et al.

[11] Patent Number: 5,965,584

[45] Date of Patent: Oct. 12, 1999

[54] PHARMACEUTICAL COMPOSITION

[75] Inventors: Hitoshi Ikeda, Higashiosaka; Takashi Sohda, Takatsuki; Hiroyuki Odaka, Kobe, all of Japan

[73] Assignee: Takeda Chemical Industries, Ltd., Osaka, Japan

[21] Appl. No.: 09/057,465

[22] Filed: Apr. 9, 1998

Related U.S. Application Data

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[30] Foreign Application Priority Data

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[51] Int. Cl.[6] A61K 31/425; A61K 31/44; A61K 45/06

[52] U.S. Cl. 514/342; 514/340; 514/365; 514/374; 546/269.7; 546/271.4; 548/146; 548/215

[58] Field of Search 546/269.7, 271.4; 514/342, 340, 365, 374; 548/146, 215

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Primary Examiner—Ziinna Northington Davis
Attorney, Agent, or Firm—Wenderoth, Lind & Ponack, L.L.P.

[57] ABSTRACT

Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with other antidiabetics differing from the enhancer in the mechanism of action, which shows a potent depressive effect on diabetic hyperglycemia and is useful for prophylaxis and treatment of diabetes.

16 Claims, No Drawings

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PHARMACEUTICAL COMPOSITION

This is a divisional application of Ser. No. 08/667,979 filed Jun. 19, 1996 now allowed.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a pharmaceutical composition comprising an insulin sensitivity enhancer in combination with one or more other antidiabetics differing from said enhancer in the mechanism of action.

2. Description of Related Art

Recent years, the pathology of diabetes has become more and more understood and, in parallel, drugs specific for the respective pathologic states have been developed. Accordingly a variety of drugs having new mechanisms of action have appeared one after another.

Insulin sensitivity enhancers are also known as insulin resistance deblockers because they have the action to normalize the impaired insulin receptor function, and are gathering much attention in these years.

Regarding such insulin sensitivity enhancers, a very useful compound such as pioglitazone has been developed [Fujita et al., Diabetes, 32, 804–810, 1983, JP-A S55(1980)-22636 (EP-A 8203), JP-A S61(1986)-267580 (EP-A 193256)]. Pioglitazone restores the impaired insulin receptor function to normalize the uneven distribution of glucose transporters in cells, the cardinal enzyme systems associated with glycometabolism, such as glucokinase, and enzyme systems associated with lipidmetabolism, such as lipoprotein lipase. As the results, insulin resistance are deblocked to improve glucose tolerance, and lower the plasma concentrations of neutral lipids and free fatty acids. Since these actions of pioglitazone are comparatively gradual and the risk of side effect in long-term administration is also low, this compound is useful for obese patients who are presumed to be highly insulin-resistant.

Also, insulin sensitivity enhancers such as CS-045, thiazolidinedione derivatives and substituted thiazolidinedione derivatives are reported to be used in combination with insulin [JP-A H4(1992)-66579, JP-A H4(1992)-69383, JP-A H5(1993)-202042]. However, the pharmaceutical composition having a specific combination of the present invention is unknown.

Diabetes is a chronic disease with diverse pathologic manifestations and is accompanied by lipidmetabolism disorders and circulatory disorders as well as glycometabolism disorders. As the results, diabetes tends to progress entailing various complications in many cases. Therefore, it is necessary to select the drug of choice for the prevailing disease state in each individual case. However, this selection is often difficult in clinical settings because single use of each individual drug can not bring sufficient effects in some disease states and there are various problems such as side effect which is caused by an increased dose or a long-term administration.

SUMMARY OF THE INVENTION

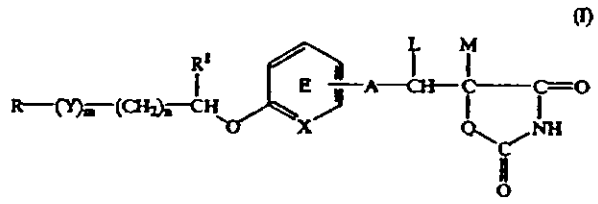
In view of the above state of the art, the inventors of the present invention did much research to develop antidiabetics which would not virtually cause adverse reactions even on long-term administration and could be effective for a large cohort of the diabetic population. As a consequence, they discovered that the above object can be accomplished by using an insulin sensitivity enhancer, such as the drug

described above, in combination with other antidiabetics differing from said enhancer in the mechanism of action, and accordingly have perfected the present invention.

The present invention, therefore, relates to:

1) Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with at least one member of the group consisting of an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor;

2) Pharmaceutical composition according to 1), wherein the insulin sensitivity enhancer is a compound represented by the formula:



(I)

wherein R represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR³— (wherein R³ represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R^1 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 substituents, and the substituents may optionally be combined with R^1 to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; or a pharmacologically acceptable salt thereof;

3) Pharmaceutical composition according to 2), wherein the compound represented by the formula (I) is pioglitazone;

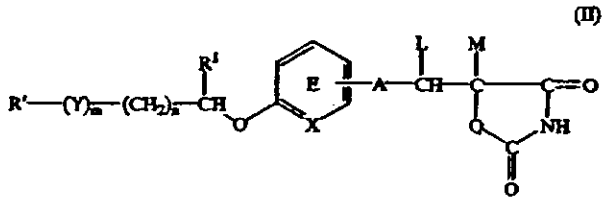
4) Pharmaceutical composition according to 1), which comprises an insulin sensitivity enhancer in combination with an α-glucosidase inhibitor;

5) Pharmaceutical composition according to 4), wherein the α-glucosidase inhibitor is voglibose;

6) Pharmaceutical composition according to 4), wherein the insulin sensitivity enhancer is pioglitazone and the α-glucosidase inhibitor is voglibose;

7) Pharmaceutical composition according to 1), which is for prophylaxis or treatment of diabetes;

8) Pharmaceutical composition which comprises a compound represented by the formula:



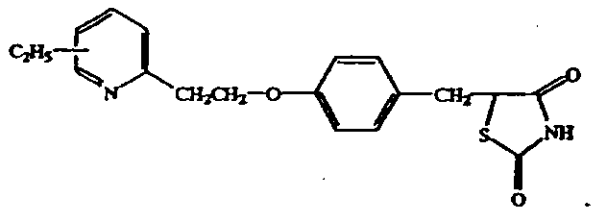
(II)

wherein R' represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR³— (wherein R³ represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R^1 represents hydrogen atom or an allyl group; ring E may optionally have 1 to 4 substituents, and

the substituents may optionally be combined with R^1 to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; with a proviso that R' does not represent benzopyranyl group when m and n are O, X represents CH, A represents a bond, Q represents sulfur atom, R^1, L and M represent hydrogen atom and ring E does not have further substituents; or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation;

9) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is the compound represented by the formula:

(III)



10) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is pioglitazone;

11) Pharmaceutical composition according to 8), wherein the insulin secretion enhancer is glibenclamide;

12) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is pioglitazone and the insulin secretion enhancer is glibenclamide;

13) Pharmaceutical composition according to 8), which is for prophylaxis or treatment of diabetes.

DETAILED DESCRIPTION OF THE INVENTION

The term "insulin sensitivity enhancer" as used in this specification means any and all drug substances that restore the impaired insulin receptor function to deblock insulin resistance and consequently enhance insulin sensitivity. As examples of the insulin sensitivity enhancer, the compound represented by the formula (I) or a pharmacologically acceptable salt thereof can be mentioned.

In the formula (I), as the hydrocarbon group in the optionally substituted hydrocarbon group represented by R, mention is made of aliphatic hydrocarbon groups, alicyclic hydrocarbon groups, alicyclic-aliphatic hydrocarbon groups, aromatic aliphatic hydrocarbon groups and aromatic hydrocarbon groups. Number of carbon atoms in these hydrocarbon groups is preferably 1 to 14.

The aliphatic hydrocarbon groups are preferably those having 1 to 8 carbon atoms. As the aliphatic hydrocarbon groups, mention is made of C_{1-8} saturated aliphatic hydrocarbon groups (e.g. alkyl group) as exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, hexyl, isohexyl, heptyl and octyl, and C_{2-8} unsaturated aliphatic hydrocarbon groups (e.g. alkenyl group, alkadienyl group, alkynyl group, alkadiynyl group) as exemplified by vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptynyl and 1-octynyl.

The alicyclic hydrocarbon groups are preferably those having 3 to 7 carbon atoms. As the alicyclic hydrocarbon groups, mention is made of C_{3-7} saturated alicyclic hydrocarbon groups (e.g. cycloalkyl group) as exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and C_{5-7} unsaturated alicyclic hydrocarbon groups (e.g. cycloalkenyl group, cycloalkadienyl group) as exemplified by 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl and 2,4-cycloheptadienyl.

As the alicyclic-aliphatic hydrocarbon groups, mention is made of, among those formed by combination of the above-mentioned alicyclic hydrocarbon groups with aliphatic hydrocarbon groups (e.g. cycloalkyl-alkyl group, cycloalkenyl-alkyl group), ones having 4 to 9 carbon atoms as exemplified by cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl and cycloheptylethyl.

The aromatic aliphatic hydrocarbon groups are preferably those having 7 to 13 carbon atoms (e.g. aralkyl group). As the aromatic aliphatic hydrocarbon groups, mention is made of C_{7-9} phenylalkyl as exemplified by benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and 1-phenylpropyl, and C_{11-13} naphthylalkyl as exemplified by α-naphthylmethyl, α-naphthylethyl, β-naphthylmethyl and β-naphthylethyl.

As the aromatic hydrocarbon groups, mention is made of, ones having 6 to 14 carbon atoms as exemplified by phenyl, naphthyl (α-naphtyl, β-naphthyl).

In the formula (I), as the heterocyclic group in the optionally substituted heterocyclic group represented by R, mention is made of, for example, 5- to 7-membered heterocyclic groups containing, as a ring component atom, 1 to 4 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom, and a condensed ring group. As the condensed ring, mention is made of, for example, these 5- to 7-membered heterocyclic groups condensed with 6-membered ring containing one or two nitrogen atoms, benzene ring or 5-membered ring containing one sulfur atom.

Examples of these heterocyclic groups include 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, 1H-indazol-3-yl, 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 1H-imidazo[4,5-b]pyrazin-2-yl and benzopyranyl. Among them, pyridyl, oxazolyl or thiazolyl group is preferable.

In the formula (I), the hydrocarbon group and heterocyclic group represented by R may-optionally have 1 to 5, preferably 1 to 3 substituents at any substitutable positions. Examples of such substituents include aliphatic hydrocarbon group, alicyclic hydrocarbon group, aryl group, aromatic heterocyclic -group, non-aromatic heterocyclic group, halogen atom, nitro group, optionally substituted amino group, optionally substituted acyl group, optionally substituted

hydroxyl group, optionally substituted thiol group, optionally esterified carboxyl group, amidino group, carbamoyl group, sulfamoyl group, sulfo group, cyano group, azido group and nitroso group.

Examples of the aliphatic hydrocarbon groups include C_{1-15} straight-chain or branched aliphatic hydrocarbon groups as exemplified by alkyl group, alkenyl group, and alkynyl group.

Preferable examples of the alkyl group include C_{1-10} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, hexyl, pentyl, octyl, nonyl and decyl.

Preferable examples of the alkenyl group include C_{2-10} alkenyl groups such as vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl.

Preferable examples of the alkynyl group include C_{2-10} alkynyl groups such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As the alicyclic hydrocarbon group, mention is made of C_{3-12} saturated or unsaturated alicyclic hydrocarbon groups as exemplified by cycloalkyl group, cycloalkenyl group and cycloalkadienyl group.

Preferable examples of cycloalkyl group include C_{3-10} cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl and bicyclo[4.3.1]decyl.

Preferable examples of the cycloalkenyl group include C_{3-10} cycloalkenyl groups such as 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl and 3-cyclohexen-1-yl.

Preferable examples of the cycloalkadienyl group include C_{4-10} cycloalkadienyl groups such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl and 2,5-cyclohexadien-1-yl.

Preferable examples of the aryl group include C_{6-14} aryl groups such as phenyl, naphthyl (1-naphthyl, 2-naphthyl), anthryl, phenanthryl and acenaphthylenyl.

Preferable examples of the aromatic heterocyclic group include aromatic monocyclic heterocyclic groups such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1;-2,3-oxadiazolyl, 1,2r4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl; and aromatic condensed heterocyclic groups such as benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolylr benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, 1,2-benzoisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, rinnolinyl, quinazolinyl, quinoxalinylr phthalazinyl, naphthylidinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenathridinyl, phenathrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, -pyrazolo[1,5-a]pyridyl, imiidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl.

Preferable examples of the non-aromatic heterocyclic group include oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidino, piperidino, morpholino and thiomorpholino.

Examples of the halogen atom include fluorine, chlorine, bromine and iodine.

As the substituted amino group in the optionally substituted amino group, mention is made of, N-monosubstituted amino group and N,N-disubstituted amino group. Examples of the substituted amino groups include amino groups having one or two substituents selected from C_{1-10} alkyl group, C_{2-10} alkenyl group, C_{2-10} alkynyl group, aromatic group, heterocyclic group and C_{1-10} acyl group (e.g. methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclohexylamino, phenylamino, N-methyl-N-phenyl-amino, acetylamino, propionylamino, benzoylamino and nicotinoylamino).

As the acyl group, mention is made of C_{1-13} acyl groups such as C_{1-10} alkanoyl group, C_{3-10} alkenoyl group, C_{4-10} cycloalkanoyl group, C_{4-10} cycloalkenoyl group and C_{6-12} aromatic carbonyl group.

Preferable examples of the C_{1-10} alkanoyl group include formyl acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl and octanoyl. Preferable examples of the C_{3-10} alkenoyl group include acryloyl, methacryloyl, crotonoyl and isocrotonoyl. Preferable examples of C_{4-10} cycloalkanoyl group include cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl and cycloheptanecarbonyl. Preferable examples of C_{4-10} cycloalkenoyl group include 2-cyclohexenecarbonyl. Preferable examples of C_{6-12} aromatic carbonyl group include benzoyl, naphthoyl and nicotinoyl.

As the substituent in the substituted acyl group, mention is made of, for example, C_{1-3} alkyl group, C_{1-3} alkoxy group, halogen atom (e.g. chlorine, fluorine, bromine, etc.), nitro group, hydroxyl group and amino group.

As the substituted hydroxyl group in the optionally substituted hydroxyl group, mention is made of, for example, alkoxy group, cycloalkyloxy group, alkenyloxy group, cycloalkenyloxy group, aralkyloxy group, acyloxy group and aryloxy group.

Preferable examples of the alkoxy group include C_{1-10} alkoxy groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, t.-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy and nonyloxy. Preferable examples of the cycloalkyloxy group include C_{3-10} cycloalkyloxy groups such as cyclobutoxy, cyclopentyloxy and cyclohexyloxy. Preferable examples of the alkenyloxy group include C_{2-10} alkenyloxy groups such as allyloxy, crotyloxy, 2-pentenyloxy and 3-hexenyloxy. Preferable examples of the cycloalkenyloxy group include C_{3-10} cycloalkenyloxy groups such as 2-cyclopentenyloxy and 2-cyclohexenyloxy. Preferable examples of the aralkyloxy group include C_{7-10} aryloxy groups such as phenyl-C_{1-4}alkyloxy (e.g. benzyloxy and phenethyloxy). Preferable examples of the acyloxy group include C_{2-13} acyloxy group, more preferably C_{2-4} alkanoyloxy groups (e.g. acetyloxy, propionyloxy, butyryloxy and isobutyryloxy). Preferable examples of the aryloxy group include C_{6-14} aryloxy groups such as phenoxy and naphthyloxy. The aryloxy group may optionally have one or two

substituents such as halogen atom (e.g. chlorine, fluorine, bromine). Examples of the substituted aryloxy group include 4-chlorophenoxy.

As the substituted thiol group in the optionally substituted thiol group, mention is made of, alkylthio group, cycloalkylthio group, alkenylthio group, cycloalkenylthio group, aralkylthio group, acylthio group and arylthio group.

Preferable examples of the alkylthio group include C_{1-10} alkylthio groups such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec.-butylthio, t.-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio and nonylthio. Preferable examples of the cycloalkylthio group include C_{3-10} cycloalkylthio groups such as cyclobutylthio, cyclopentylthio and cyclohexylthio. Preferable examples of the alkenylthio group include C_{2-10} alkenylthio groups such as allylthio, crotylthio; 2-pentenylthio and 3-hexenylthio. Preferable examples of the cycloalkenylthio group include C_{3-10} cycloalkenylthio groups such as 2-cyclopentenylthio and 2-cyclohexenylthio. Preferable examples of the aralkylthio include C_{7-10} aralkylthio groups such as phenyl-C_{1-4}alkylthio (e.g. benzylthio and phenethylthio). Preferable examples of the acylthio group include C_{2-13} acylthio group, more preferably C_{2-4} alkanoylthio groups (e.g. acetylthio, propionylthio, butyrylthio and isobutyrylthio).

Preferable examples of the arylthio group include C_{6-14} arylthio groups such as phenylthio and naphthylthio. The arylthio group may optionally have one or two substituents such as halogen atom (e.g. chlorine, fluorine, bromine). Examples of the substituted arylthio group include 4-chlorophenylthio.

As the optionally esterified carboxyl group, mention is made of, for example, alkoxycarbonyl group, aralkyloxy carbonyl group and aryloxycarbonyl group.

Preferable examples of the alkoxycarbonyl group include C_{2-5} alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and butoxycarbonyl. Preferable examples of the aralkyloxycarbonyl group include C_{8-10} aralkyloxycarbonyl groups such as benzyloxycarbonyl. Preferable examples of the aryloxycarbonyl group include C_{7-15} aryloxycarbonyl groups such as phenoxycarbonyl and p-tolyloxycarbonyl.

Among the substituents on the hydrocarbon group and heterocyclic group represented by R, C_{1-10} alkyl groups, aromatic heterocyclic groups and C_{6-14} aryl groups are preferable, and C_{1-3} alkyl, furyl, thienyl, phenyl and naphthyl are especially preferable.

In the formula (I), substituents on the hydrocarbon group and heterocyclic group which are represented by R, may, when they are alicyclic hydrocarbon group, aryl group, aromatic heterocyclic group or non-aromatic heterocyclic group, have one or more, preferably 1 to 3, of suitable substituents respectively. Examples of these substituents include C_{1-6} alkyl groups, C_{2-6} alkenyl groups, C_{2-6} alkynyl groups, C_{3-7} cycloalkyl groups, C_{6-14} aryl groups, aromatic heterocyclic groups (e.g. thienyl, furyl, pyridyl, oxazolyl and thiazolyl), non-aromatic heterocyclic groups (e.g. tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolidino and piperazino), C_{7-9} aralkyl groups, amino group, N-mono-C_{1-4} alkylamino groups, N,N-di-C_{1-4} alkylamino groups, C_{2-8} acylamino groups (e.g. acetylamino, propionylamino and benzoylamino), amidino group, C_{2-8} acyl group (e.g. C_{2-8} alkanoyl groups), carbamoyl group, N-mono-C_{1-4} alkyl carbamoyl groups, N,N-di-C_{1-4} alkyl carbamoyl groups, sulfamoyl group, N-mono-C_{1-4} alkyl sulfamoyl groups, N,N-di-C_{1-4} alkyl sulfamoyl groups, carboxyl group, C_{2-8} alkoxycarbonyl groups, hydroxyl group, C_{1-4} alkoxy groups, C_{2-5} alkenyloxy groups, C_{3-7} cycloalkyloxy groups, C_{7-9} aralkyloxy groups, C_{6-14} aryloxy groups, mercapto group, C_{1-4} alkylthio groups, C_{7-9} aralkylthio groups C_{6-14} arylthio groups, sulfo group, cyano group, azido group, nitro group, nitroso group and halogen atom.

In the formula (I), R is preferably an optionally substituted heterocyclic group. R is more preferably pyridyl, oxazolyl or thiazolyl group which is optionally substituted by 1 to 3 substituents selected from C_{1-3} alkyl group, furyl group, thienyl group, phenyl group and naphthyl group.

R' in the formula (II) has the same definition as R except that R' does not represent benzopyranyl group when m and n are O; X represents CH; A represents a bond; Q represents sulfur atom; R', L and M represent hydrogen atom; and ring E does not have further substituents.

In the formulae (I) and (II), Y represents —CO—, —CH(OH)— or —NR^3— (wherein R represents an optionally substituted alkyl group), preferably —CH(OH)— or —NR^3—. As the alkyl group in the optionally substituted alkyl group represented by R^3, mention is made of, for example, C_{1-4} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl and t.-butyl. Examples of the substituents include halogen (e.g., fluorine, chlorine, bromine and iodine), C_{1-4} alkoxy groups (e.g. methoxy, ethoxy, propoxy, butoxy, isobutoxy, sec.-butoxy and t.-butoxy), hydroxyl group, nitro group and C_{1-4} acyl groups (e.g. formyl, acetyl and propionyl).

The symbol m is 0 or 1, preferably 0.

The symbol n is 0, 1 or 2, preferably 0 or 1.

X represents CH or N, preferably CH.

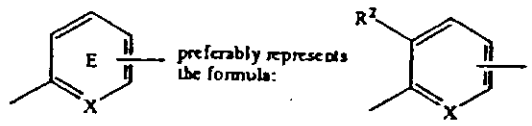
In the formulae (I) and (II), A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group The aliphatic hydrocarbon group may be straight-chain or branched, and saturated or unsaturated. Specific examples of the aliphatic hydrocarbon group include saturated ones [e.g. —CH_2—, —$CH(CH_3)$—, —$(CH_2)_2$—, —$CH(C_2H_5)$—, —$(CH_2)_3$—, —$(CH_2)_4$—, —$(CH_2)_5$—, —$(CH_2)_6$— and —$(CH_2)_7$—] and unsaturated ones [e.g. —CH=CH—, —$C(CH_3)$=CH—, —CH=CH—CH_2—, —$C(C_2H_5)$=CH—, —CH_2—CH=CH—CH_2—, —CH_2—CH_2—CH=CH—CH_2—. —CH=CH—CH=CH—CH_2— and —CH=CH—CH=CH—CH=CH—CH_2—]. A is preferably a bond or C_{1-4} divalent aliphatic hydrocarbon groups, the aliphatic hydrocarbon groups preferably being saturated. A is more preferably a bond or —$(CH_2)_2$—.

As the alkyl group represented by R^1, substantially the same one as the alkyl group in the above-mentioned R^3. R^1 is preferably hydrogen atom.

In the formulae (I) and (II), the partial formula:

Ring E has 1 to 4 substituents at any substitutable positions. Examples of such substituents include alkyl group, optionally substituted hydroxyl group, halogen atom, optionally substituted acyl group and optionally substituted amino group. These substituents have substantially the same meaning as those described as substituents of the hydrocarbon group and heterocyclic group represented by R.

Ring E, namely the partial formula:



wherein R^2 represents hydrogen atom, an alkyl group, an optionally substituted hydroxyl group, a halogen atom, an optionally substituted acyl group, nitro group or an optionally substituted amino group.

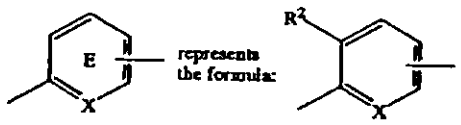
As the alkyl group, optionally substituted hydroxyl group, halogen atom, optionally substituted acyl group and optionally substituted amino group represented by R^2, mention is made of those described as substituents of the hydrocarbon group and heterocyclic group represented by R. R^2 is preferably hydrogen atom, optionally substituted hydroxyl group or halogen atom, more preferably hydrogen atom or optionally substituted hydroxyl group, especially preferably hydrogen atom or C_{1-4} alkoxy groups.

In the formulae (I) and (II), L and M represent hydrogen atom, or they may optionally be combined with each other to form a bond. L and M are preferably hydrogen atom.

In the compounds wherein L and M are combined with each other to form a bond, there exist (E)—and (Z)— isomers relative to the double bond at the 5-position of the azolidinedione ring.

And, in the compounds wherein L and M respectively represent hydrogen atom, there exist (R)— and (S)— optical isomers due to the asymmetric carbon at the 5-position of the azolidinedione ring. The compounds include these (R)— and (S)— optical isomers and racemic isomers.

Preferable examples of the compounds represented by the formula (I) or (II) includes those in which R is pyridyl, oxazolyl or thiazolyl group optionally having 1 to 3 substituents selected from C_{1-3} alkyl, furyl, thienyl, phenyl and naphthyl; m is 0; n is 0 or 1; X is CH; A is a bond or $—(CH_2)_2—$; R^1 is hydrogen atom; ring E, namely the partial formula:



and R^2 is hydrogen atom or C_{1-4} alkoxy group; and L and M are both hydrogen atom.

Preferable examples of the compound represented by the formula (I) include

(1) the compound represented by the formula (III) such as 5-[4-[2—(3-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione; 5-[4-[2—(4-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione; 5-[4-[2—(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (generic name: pioglitazone); and 5-[4-[2—(6-ethyl-2-pyridyl)-ethoxy]benzyl]-2,4-thiazolidinedione;

(2) (R)—(+)-5-[3-[4-[2—(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione; and

(3) 5-[[4—((3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (generic name: troglitazo tCS-045).

The compound represented by the formula (I) is especially preferably pioglitazone.

The compound represented by the formula (II) is preferably the compound represented by the formula (III) and (R)—(+)-5-[3-[4-[2—(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione, more preferably pioglitazone.

The pharmacologically acceptable salt of the compound represented by the formula (I) or (II) are exemplified by salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

Preferable examples of salts with inorganic bases include salts with alkali metals such as sodium, potassium, etc., salts with alkaline earth metals such as calcium, magnesium, etc., and salts with aluminum, ammonium, etc.

Preferable examples of salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, etc.

Preferable examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.

Preferable examples of salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.

Preferable examples of salts with basic amino acids include salts with arginine, lysine, ornithine, etc., and preferable examples of salts with acidic amino acids include salts with aspartic acid, glutamic acid, etc.

The pharmacologically acceptable salt of the compound represented by the formula (III) is preferably a salt with an inorganic acid, more preferably a salt with hydrochloric acid. Especially, pioglitazone is preferably used in the form of salt with hydrochloric acid.

The compounds represented by the formula (I) or (II) or a salt thereof can be produced in accordance with, for example, methods described in JPA S55(1980)-22636(EP-A 8203), JPA S60(1985)-208980(EP-A 155845), JPA S61(1986)-286376(EP-A 208420), JPA S61(1986)-85372(EP-A 177353), JPA S61(1986)-267580(EP-A 193256), JPA H5(1993)-86057(WO 92/18501), JPA H7(1995)-82269 (EP-A 605228), JPA H7(1995)-101945(EP-A 612743), EP-A 643050, EP-A 710659, etc. or methods analogous thereto.

Insulin sensitivity enhancers include 5-[[3,4-dihydro-2-(phenylmethyl)-2H-1-benzopyran-6-yl]methyl]-2,4-thiazolidinedione (generic name: englitazone) or its sodium salt;

5-[[4-[3—(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl]phenyl]methyl]-2,4-thiazolidinedione (generic name: darglitazone/CP-86325) or its sodium salt;

5-[2—(5-methyl-2-phenyl-4-oxazolylmethyl)benzofuran-5-ylmethyl]-2,4-oxazolidinedione (CP-92768);

5—(2-naphthalenylsulfonyl)-2,4-thiazolidinedione (AY-31637);

4-[(2-naphthalenyl)methyl]-3H-1,2,3,5-oxathiadiazol-2-oxide (AY-30711); and

5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]-methyl]-2,4-thiazolidinediore (BRL-49653), etc. in addition to compounds mentioned hereinbefore.

In the present invention, examples of the drug which is used in combination with the above-mentioned insulin sensitivity enhancer include an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor.

α-Glucosidase inhibitors are drugs which inhibit digestive enzymes such as amylase, maltase, α-dextrinase, sucrase, etc. to retard digestion of starch and sugars. Examples of the α-glucosidase inhibitors include acarbose, N-(1,3-dihydroxy-2-propyl)valiolamine (generic name; voglibose), miglitol, etc. with preferance given to voglibose.

Aldose reductase inhibitors are drugs which inhibit the first-stage rate-limiting enzyme in the polyol pathway to prevent or arrest diabetic complications. In the hyperglycemic state of diabetes, the utilization of glucose in the polyol pathway is increased and the excess sorbitol accumulated intracellularly as a consequence acts as a tissue toxin and hence evokes the onset of complications such as diabetic neuropathy, retinopathy, and nephropathy. Examples of the aldose reductase inhibitors include tolurestat; epalrestat; 3,4-dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxazine-4-acetic acid; 2,7-difluoro-spiro(9H-fluorene-9,4'-imidazolidine)-2',5'-dione (generic name: imirestat); 3-[(4-bromo-2-fluorophenyl)methyl]-7-chloro-3,4-dihydro-2,4-dioxo-1(2H)-quinazoline acetic acid (generic name: zenarestat); 6-fluoro-2,3-dihydro-2',5'-dioxo-spiro[4H-1-benzopyran-4,4'-imidazolidine]-2-carboxamide (SNK-860); zopolrestat; sorbinil; and 1-[(3-bromo-2-benzofuranyl)sulfonyl]-2,4-imidazolidinedione (M-16209), etc.

Biguanides are drugs having actions of stimulation of anaerobic glycolysis, increase of the sensitivity to insulin in the peripheral tissues, inhibition of glucose absorption from the intestine, suppression of hepatic gluconeogenesis, and inhibition of fatty acid oxidation. Examples of the biguanides include phenformin, metformin, buformin etc.

Statin compounds are drugs having actions of lowering blood cholesterol levels by inhibiting hydroxymethylglutalyl CoA (HMG—CoA) reductase. Examples of the statin compounds include pravastatin and its sodium salt, simvastatin, lovastatin, atorvastatin, fluvastatin, etc.

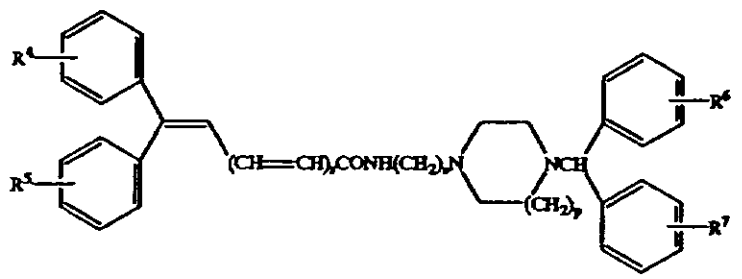
Squalene synthesis inhibitors are drugs having actions of lowering blood cholesterol levels by inhibiting synthesis of squalene. Examples of the squalene synthesis inhibitors include (S)-α-[Bis[2,2-dimethyl-1-oxopropoxy)methoxy] phosphinyl]-3-phenoxybenzenebutanesulfonic acid, monopotassium salt (BMS-188494).

Fibrate compounds are drugs having actions of lowering blood cholesterol levels by inhibiting synthesis and secretion of triglycerides in liver and activating a lipoprotein lipase.

Examples of the fibrate compounds include bezafibrate, beclobrate, binifibrate, ciplofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate, etc.

LDL catabolism enhancers are drugs having actions of lowering blood cholesterol levels by increasing the number of LDL (low-density lipoprotein) receptors.

Examples of the LDL catabolism enhancers include the compound which is described in JPA H7(1995)-316144, and represented by the formula:



wherein R^4, R^5, R^6 and R^7 are the same or different, and represent hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group; r is 0–2; is 2–4; p is 1–2; or a salt thereof; specifically N-[2-[4-bis(4-fluorophenyl) methyl-1-piperazinyl]ethyl]-7,7-dipbenyl-2,4,6-heptatrienic acid amide, etc.

The above-mentioned statin compounds, squalene synthesis inhibitors, fibrate compounds and LDL catabolism enhancers can be substituted with other drugs having the property to lower blood cholesterol and triglyceride levels. Examples of these drugs include nicotinic acid derivatives such as nicomol and niceritrol; antioxidants such as probucol; and ion-exchange resins such as colestyramin.

Angiotensin converting enzyme inhibitors are drugs having actions of partially lowering blood glucose levels as well as lowering blood pressure by inhibiting angiotensin converting enzymes. Examples of the angiotensin converting enzyme inhibitors include captopril, enalapril, alacepril, delapril, ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moveltopril, perindopril, quinapril, spirapril, temocapril, trandolapril, etc.

In the present invention, especially preferred is the pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with an α-glucosidase inhibitor. The insulin sensitivity enhancer is especially preferably pioglita zone, and the α-glucosidase inhibitor is especially preferably voglibose.

In the present invention, examples of the drug which is used in combination with the compound represented by the formula (II) or a pharmacologically acceptable salt thereof include an insulin secretion enhancer and/or an insulin preparation.

Insulin secretion enhancers are drugs having the property to promote secretion of insulin from pancreatic β cells. Examples of the insulin secretion enhancers include sulfonylureas (SU). The sulfonylureas (SU) are drugs which promote secretion of insulin from pancreatic β cells by transmitting signals of insulin secretion via SU receptors in the cell membranes. Examples of the SU include tolbutamide; chlorpropamide; tolazamide; acetohexamide; 4-chloro-N-[(1-pyrolidinylamino)carbonyl]-benzenesulfonamide (generic name: glycopyramide) or its ammonium salt; glibenclamide (glyburide); gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; tolcyclamide, etc.

Insulin secretion enhancers include N-[[4-(1-methylethyl) cyclobexyl)carbonyl]-D-phenylalanine (AY-4166); calcium (2S)-2-benzyl-3—(cis-hexahydro-2-isoindolinylcarbonyl) propionate dihydrate TKAD-1229); and glimepiride (Hoe 490), etc. in addition to compounds mentioned hereinbefore. The insulin secretion enhancer is especially preferably glibenclamide.

Examples of the insulin preparations include animal insulin preparations typically extracted from bovine or porcine

pancreas and human insulin preparations synthesized by genetic engineering techniques typically using *Escherichia coli* or yeasts. While insulin preparations are available in a variety of types, e.g. immediate-acting, bimodal-acting, intermediate-acting, and long-acting, these types of preparations can be selectively administered according to the patient's condition.

In the present invention, especially preferred is - the pharmaceutical composition which comprises the compound represented by the formula (II) or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer. The compound represented by the formula (II) or a pharmacologically acceptable salt thereof is especially preferably pioglitazone, and the insulin secretion enhancer is especially preferably glibenclamide.

The pharmaceutical composition comprising an insulin sensitivity enhancer in combination with at least one member selected from the group consisting of an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor; and the pharmaceutical composition comprising the compound represented by the formula (II) or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation, both provided in accordance with the present invention, can be respectively put to use by mixing the respective active components either all together or independently with a physiologically acceptable carrier, excipient, binder, diluent, etc. and administering the mixture or mixtures either orally or non-orally as a pharmaceutical composition. When the active components are formulated independently, the respective formulations can be extemporaneously admixed using a diluent or the like and administered or can be administered independently of each other, either concurrently or at staggered times to the same subject.

The dosage form for said pharmaceutical composition includes such oral dosage forms as granules, powders, tablets, capsules, syrups, emulsions, suspensions, etc. and such non-oral dosage forms as injections (e.g. subcutaneous, intravenous, intramuscular and intraperitoneal injections), drip infusions, external application forms (e.g. nasal spray preparations, transdermal preparations, ointments, etc.), and suppositories (e.g. rectal and vaginal suppositories).

These dosage forms can be manufactured by the per se known technique conventionally used in pharmaceutical procedures. The specific manufacturing procedures are as follows.

To manufacture an oral dosage form, an excipient (e.g. lactose, sucrose, starch, mannitol, etc.), a disintegrator (e.g. calcium carbonate, carboxymethylcellulose calcium, etc.), a binder (e.g. α-starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, etc.), and a lubricant (e.g. talc, magnesium stearate, polyethylene glycol 6000, etc.), for instance, are added to the active component or components and the resulting composition is compressed. Where necessary, the compressed product is coated, by the per se known technique, for masking the taste or for enteric dissolution or sustained release. The coating material that can be used includes, for instance, ethylcellulose, hydroxymethylcellulose, polyoxyethylene glycol, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, and Eudragit (Rohm & Haas, Germany, methacrylic-acrylic copolymer).

Injections can be manufactured typically by the following procedure. The active component or components are dissolved, suspended or emulsified in an aqueous vehicle (e.g. distilled water, physiological saline, Ringer's solution, etc.) or an oily vehicle (e.g. vegetable oil such as olive oil, sesame oil, cottonseed oil, corn oil, etc. or propylene glycol) together with a dispersant (e.g. Tween 80 (Atlas Powder, U.S.A.), HCO 60 (Nikko Chemicals), polyethylene glycol, carboxymethylcellulose, sodium alginate, etc.), a preservative (e.g. methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, benzyl alcohol, chlorobutanol, phenol, etc.), an isotonizing agent (e.g. sodium chloride, glycerol, sorbitol, glucose, inverted sugar, etc.) and other additives. If desired, a solubilizer (e.g. sodium salicylate, sodium acetate, etc.), a stabilizer (e.g. human serum albumin), a soothing agent (e.g. benzalkonium chloride, procaine hydrochloride, etc.) and other additives can also be added.

A dosage form for external application can be manufactured by processing the active component or components into a solid, semi-solid or liquid composition. To manufacture a solid composition, for instance, the active component or components, either as they are or in admixture with an excipient (e.g. lactose, mannitol, starch, microcrystalline cellulose, sucrose, etc.), a thickener (e.g. natural gums, cellulose derivatives, acrylic polymers, etc.), etc., are processed into powders. The liquid composition can be manufactured in substantially the same manner as the injections mentioned above. The semi-solid composition is preferably provided in a hydrous or oily gel form or an ointment form. These compositions-may optionally contain a pH control agent (e.g. carbonic acid, phosphoric acid, citric acid, hydrochloric acid, sodium hydroxide, etc.), and a preservative (e.g. p-hydroxybenzoic acid esters, chlorobutanol, benzalkonium chloride, etc.), among other additives.

Suppositories can be manufactured by processing the active component or components into an oily or I aqueous composition, whether solid, semi-solid or liquid. The oleaginous base that can be used includes, for instance, higher fatty acid glycerides [e.g. cacao butter, Witepsols (Dinamit-Nobel), etc.], medium-chain fatty acids [e.g. Migriols (Dinamit-Nobel), etc.], vegetable oils (e.g. sesame oil, soybean oil, cotton-seed oil, etc.), etc. The water-soluble base includes, for instance, polyethylene glycols, propylene glycol, etc. The hydrophilic base includes, for instance, natural gums, cellulose derivatives, vinyl polymers, and acrylic polymers, etc.

The pharmaceutical composition of the present invention is low in toxicity and can be safely used in mammals (e.g. humans, mice, rats, rabbits, dogs, cats, bovines, horses, swines, monkeys).

The dosage of the pharmaceutical composition of the present invention may be appropriately determined with reference to the dosages recommended for the respective active components and can be selected appropriately according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of the active components, among other factors. For example, the dosage of the insulin sensitivity enhancer for an adult can be selected from the clinical oral dose range of 0.01 to 10 mg/kg body weight (preferably 0.05 to 10 mg/kg boday weight, more preferably 0.05 to 5 mg/kg body weight) or the clinical parenteral dose range of 0.005 to 10 mg/kg body weight (preferably 0.01 to 10 mg/kg body weight, more preferably 0.01 to 1 mg/kg body weight). The other active component or components having different modes of action for use in combination can also be used in dose ranges selected by referring to the respective recommended clinical dose ranges. The preferred frequency of administration is 1 to 3 times a day.

The proportions of the active components in the a pharmaceutical composition of the present invention can be appropriately selected according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of active components, among other factors. When, for example, the compound represented by the formula (I) or a pharmacologically acceptable salt thereof (e.g. pioglitazone) which is the insulin sensitivity enhancer and voglibose which is an α-glucosidase inhibitor are to be administered in combination to a human subject, voglibose is used in a proportion of usually about 0.0001 to 0.2 weight parts and preferably about 0.001 to 0.02 weight parts relative to 1 weight part of the compound or a salt thereof. When, for example, the compound represented by the formula (II) or a pharmacologically acceptable salt thereof and glibenclamide which is an insulin secretion enhancer are to be administered in combination to a human subject, glibenclamide is used in a proportion of usually about 0.002 to 5 weight parts and preferably about 0.025 to 0.5 weight parts, relative to 1 weight-part of the compound or a pharmacologically acceptable salt thereof.

The pharmaceutical composition of the-present invention shows a marked synergistic effect compared with administration of either active component alone. For example, compared with cases in which each of these active components was administered to diabetic wistar fatty rats with genetical obsesity, administration of these active components in combination resulted in marked improvements in both hyperglycemia and reduced glucose tolerance. Thus, the pharmaceutical composition of the present invention lowers blood glucose in diabetics more effectively than it is the case with administration of each component drug alone and, therefore, can be used advantageously for the prophylaxis and treatment of diabetic complications.

Furthermore, since the pharmaceutical composition of the present invention develops sufficient efficacy with reduced doses as compared with the administration of any one of the active components alone, the side effects of the respective components (e.g. gastrointestinal disorders such as diarrhea, etc.) can be reduced.

The following working examples and experimental examples are merely intended to illustrate the present invention in further detail but should by no means be construed as defining the scope of the invention.

The pharmaceutical composition of the present invention can be prepared according to the following formulations.

WORKING EXAMPLE 1

Capsules	
(1) Pioglitazone hydrochloride	30 mg
(2) Voglibose	0.2 mg
(3) Lactose	60 mg
(4) Microcrystalline cellulose	79.8 mg
(5) Magnesium stearate	10 mg
Total	180 mg

The whole amounts of (1), (2), (3) and (4) and half the amount of (5) are mixed well and granulated in the conventional manner. Then, the balance of (5) is added and, after mixing, the whole composition is filled in a gelatin hard capsule shell.

WORKING EXAMPLE 2

Tablets	
(1) Pioglitazone hydrochloride	10 mg
(2) Glibenclamide	1.25 mg
(3) Lactose	86.25 mg
(4) Corn starch	20 mg
(5) Polyethylene glycol	2.5 mg
(6) Hydroxypropylcellulose	4 mg
(7) Carmellose calcium	5.5 mg
(9) Magnesium stearate	0.5 mg
	130 mg (per tablet)

The whole amounts of (1), (2), (3), (4), and (5), ⅗ amounts of (6) and (7), and ½ amount of (8) are mixed well and granulated in the conventional manner. Then, the balances of (6), (7) and (8) are added to the granules, which is mixed well and the whole composition is compressed with a tablet machine. The adult dosage is 3 tablets/day, to be taken in 1 to 3 divided doses.

WORKING EXAMPLE 3

Capsules	
(1) Pioglitazone hydrochloride	10 mg
(2) Epalrestat	50 mg
(3) Lactose	55 mg
(4) Microcrystalline cellulose	55 mg
(5) Magnesium stearate	10 mg
Total	180 mg

The whole amounts of (1), (2), (3) and (4) and ½ amount of (5) are mixed well and granulated in the conventional manner. Then, the balance of (5) is added and the whole composition is filled in gelatin capsule shell. The adult dosage is 3 capsules/day, to be taken in 1 to 3 divided doses.

EXPERIMENTAL EXAMPLE 1

Effect of pioglitazone hydrochloride in combination with α-glucosidase inhibitor in genetically obese and diabetic Wistar fatty rats

Male Wistar fatty rats aged 14–19 weeks were divided into 4 groups of 5–6, and pioglitazone hydrochloride (1 mg/kg body wt./day, p.o.) and/or voglibose (an α-glucosidase inhibitor) (0.31 mg/kg body wt./day; administered by mixing in commercial diet at a rate of 5 ppm) was administered for 14 days. The blood was then collected from the tail vein and the plasma glucose and hemoglobin Al were determined by the enzymatic method (Encore Chemical System, Baker) and using a commercial kit (NC-ROPET, Nippon Chemiphar Co.), respectively. The results were expressed in mean ± standard deviation for each group (n=5–6) and analyzed by Dunnett's test, which are shown in Table 1. The 1% level of significance was used.

TABLE 1

Group	Plasma glucose (mg/dl)	Hemoglobin A_1 (%)
Control	345 ± 29	5.7 ± 0.4
Pioglitazone	215 ± 50*	5.2 ± 0.3
Voglibose	326 ± 46	6.0 ± 0.6
Pioglitazone + voglibose	114 ± 23*	4.5 ± 0.4*

*P < 0.01 vs. control group

It is apparent from Table 1 that both the blood glucose and hemoglobin A, levels were remarkably lowered by com-

bined administration of pioglitazone and voglibose as compared with the administration of either drug alone.

EXPERIMENTAL EXAMPLE 2

Effect of pioglitazone hydrochloride in combination with an insulin secretion enhancer in genetically obese and diabetic Wistar fatty rats

Male Wistar fatty rats aged 13–14 weeks were divided into 4 groups of 5, and pioglitazone hydrochloride (3 mg/kg/day, p.o.) and/or glibenclamide (an insulin secretion enhancer) (3 mg/kg/day, p.o.) was administered for 7 days. Following an overnight fast, the oral glucose loading test (2 g glucose/kg/5 ml, p.o.) was carried out. Prior to glucose loading and 120 and 240 minutes after the loading, blood was collected from the tail vein and the plasma glucose was assayed by the enzymatic method (Encore Chemical System, Baker). The results were expressed in mean ± SD for each group (n=5) and analyzed by Dunnett's test, which are shown in Table 2.

TABLE 2

	Plasma glucose (mg/dl)		
Group	0 min.	120 min.	240 min.
Control	119 ± 9	241 ± 58	137 ± 10
Pioglitazone	102 ± 12	136 ± 17*	102 ± 9*
Glibenclamide	118 ± 12	222 ± 61	106 ± 24*
Pioglitazone + glibenclamide	108 ± 3	86 ± 10*	60 ± 5*

*P < 0.01 vs. control group

It is apparent from Table 2 that the increase of blood sugar following glucose loading was remarkably inhibited by the combined administration of pioglitazone and glibenclamide as compared with the administration of either drug alone.

The pharmaceutical composition of the present invention shows a potent depressive effect on diabetic hyperglycemia and is useful for prophylaxis and treatment of diabetes. Moreover, this pharmaceutical composition is useful for prophylaxis and treatment of diabetic complications such as diabetic neuropathy, nephropathy, retinopathy, macroangiopathy, and osteopenia. In addition, by appropriately selecting the kinds of component drugs, administration route, dosage, etc. according to clinical status, stable hypoglycemic efficacy in long-term therapy can be expected with an extremely low risk of side effect.

What is claimed is:

1. A pharmaceutical composition comprising an insulin sensitivity enhancer In combination with a biguanide, wherein the insulin sensitivity enhancer is selected from the group consisting of:

(1) 5-(4-(2-(3-ethyl-2-pyridyl)ethoxy)benzyl]-2,4-thiazolidinedione or its pharmacologically acceptable salt,

(2) 5-(4-(2-(4-ethyl-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione or its pharmacologically acceptable salt,

(3) 5-(4-(2-(5-ethyl-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione or its pharmacologically acceptable salt,

(4) 5-(4-(2-(6-ethyl-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione or its pharmacologically acceptable salt,

(5) (R)-(+)-5-(3-(4-(2-(2-furyl)-5-methyl-4-oxazolylmethoxy)-3-methoxyphenyl)propyl)-2,4-oxazolidinedione or its pharmacologically acceptable salt.

(6) 5-((3,4-dihydro-2-(phenylmethyl)-2H-1-benzopyran-6-yl)methyl)-2,4thiazolidinedione or its sodium salt,

(7) 5-((4-(3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl)phenyl)methyl)-2,4-thiazolidinedione or its sodium salt.

(8) 5-(2-(5-methyl-2-phenyl-4-oxazolylmethyl) benzofuran-5-ylmethyl)-2,4-oxazolidinedione,

(9) 5-(2-naphthalenylsulfonyl)-2,4-thiazolidinedione, and

(10) 5-((4-(2-methyl-2-pyridylamino)ethoxy)phenyl)-methyl)-2,4-thiazolidinedione or its pharmacologically acceptable salt.

2. The pharmaceutical composition according to claim 1, wherein the insulin sensitivity enhancer is pioglitazone or its hydrochloride.

3. The pharmaceutical composition according to claim 1, wherein the biguanide is selected from the group consisting of phenformin, metformin, and buformin.

4. The pharmaceutical composition according to claim 1, wherein the insulin sensitivity enhancer is pioglitazone or its hydrochloride and the biguanide is metformin.

5. The pharmaceutical composition according to claim 1, which is for treatment of diabetes.

6. A method for treating diabetes in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of an insulin sensitivity enhancer in combination with a biguanide, wherein the insulin sensitivity enhancer is selected from the group consisting of:

(1) 5-(4-(2-(3-ethyl-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione or its pharmacologically acceptable salt,

(2) 5-(4-(2-(4-ethyl-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione or its pharmacologically acceptable salt,

(3) 5-(4-(2-(5-ethyl-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione or its pharmacologically acceptable salt,

(4) 5-(4-(2-(6-ethyl-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione or its pharmacologically acceptable salt,

(5) (R)—(+)-5-(3-(4-(2 -(2-furyl)-5-methyl-4-oxazolylmethoxy)-3-methoxyphenyl)propyl-2,4-oxazolidinedione or its pharmacologically acceptable salt,

(6) 5-((3,4-dihydro-2-(phenylmethyl)-2H-1-benzopyran-6-yl)methyl)-2,4-thiazolidinedione or its sodium salt.

(7) 5-((4-(3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl)phenyl)methyl)-2,4-thiazolidinedione or its sodium salt,

(8) 5-(2-(5-methyl-2-phenyl-4-oxazolylmethyl) benzofuran-5-ylmethyl)-2,4-oxazolidinedione,

(9) 5-(2-naphthalenylsulfonyl)-2,4-thiazolidinedione, and

(10) 5-((4-(2-methyl-2-pyridylamino)ethoxy)phenyl)-methyl)-2,4-thiazolidinedione or its pharmacologically acceptable salt.

7. The method according to claim 6, wherein the insulin sensitivity enhancer is pioglitazone or its hydrochloride.

8. The method according to claim 6, wherein the biguanide is selected from the group consisting of phenformin, metformin and buformin.

9. The method according to claim 6, wherein the biguanide is metformin.

10. The method according to claim 6, wherein the insulin sensitivity enhancer is pioglitazone or its hydrochloride and the biguanide is metformin.

11. The pharmaceutical composition according to claim 1, wherein the insulin sensitivity enhancer is 5-((4-(2-methyl-2-pyridylamino)ethoxy)phenyl)-methyl)-2,4-thiazolidinedione or its pharmacologically acceptable salt.

12. The method according to claim 6, wherein the insulin sensitivity enhancer is 5-((4-(2-methyl-2-pyridylamino) ethoxy)phenyl)-methyl)-2,4-thiazolidinedione or its pharmacologically acceptable salt.

13. The method according to claim 6, wherein the insulin sensitivity enhancer and the biguanide are mixed together to form an admixture and the admixture is administered to the mammal.

14. The method according to claim 6, wherein the insulin sensitivity enhancer and the biguanide are not mixed together to form an admixture but are administered independently to the mammal.

15. The composition according to claim 1, wherein the composition consists of the insulin sensitivity enhancer and biguanide.

16. The method according to claim 6, with the proviso that the mammal is not administered a sulfonylurea agent.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,965,584
DATED : October 12, 1999
INVENTOR(S) : Hitoshi IKEDA et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 5, line 51, change "1;-2,3" to --1,2,3--;
line 52, change "1,2r4" to --1,2,4--;
line 60, change "rinnolinyl" to --cinnolinyl--;
line 61, change "quinoxalinylr" to --quinoxalinyl--;
line 66, delete the dash (-) before "pyrazolo"; change "imiidazo" to --imidazo--.

Column 8, line 16, change the term "R'" to --R^1--;
line 19, change "R represents" to --R^3 represents--;

Column 9, line 58, change "methoxyphenylJpropyl" to read --methoxyphenyl]propyl--;
line 60, change "((3,4" to read --[(3,4--;
line 62, change "troglitazo tCS-045" to read --troglitazone/CS-045--.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,965,584
DATED : October 12, 1999
INVENTOR(S) : Hitoshi IKEDA et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 12,line 1, change "is 2-4" should read --s is 2-4--;

line 23, change "pioglita zone" to --pioglitazone--;

line 48, change "TKAD" to --(KAD--.

Column 13, line 8, delete the dash (-) after the term "is".

Column 14, line 27, delete the dash (-) after the term "compositions";

line 33, delete "I" before "aqueous";

line 58, change "boday" to --body--.

Column 15, line 24, delete the dash (-) before "present".

Column 16, line 49, change "hemoglobin A1" to --hemoglobin A_1--;

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,965,584
DATED : October 12, 1999
INVENTOR(S) : Hitoshi IKEDA et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 16, line 61, in Table 1, middle column, change "215 ± 50°" to read --215 ± 50°--;

line 67, change "hemoglobin A," to --hemoglobin A_1--.

Column 17, line 48, change "In" to --in--.

Column 18, line 2, change "2,4thiazolidinedione" to --2,4-thiazolidinedione--;

line 9, change "2-methyl" to read --2-(methyl--;

line 55, change "2-methyl" to read --2-(methyl--.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,965,584
DATED : October 12, 1999
INVENTOR(S) : Hitoshi IKEDA et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 19, line 2, change "2-methyl" to --2-(methyl--.
line 6, change "2-methyl" to --2-(methyl--.

Signed and Sealed this

Nineteenth Day of December, 2000

Attest:

Attesting Officer

Q. TODD DICKINSON

Commissioner of Patents and Trademarks

B

US006329404B1

(12) **United States Patent**
Ikeda et al.

(10) **Patent No.: US 6,329,404 B1**
(45) **Date of Patent: Dec. 11, 2001**

(54) **PHARMACEUTICAL COMPOSITION**

(75) Inventors: **Hitoshi Ikeda**, Higashiosaka; **Takashi Sohda**, Takatsuki; **Hiroyuki Odaka**, Kobe, all of (JP)

(73) Assignee: **Takeda Chemical Industries, Ltd.**, Osaka (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/453,521**

(22) Filed: **Dec. 3, 1999**

Related U.S. Application Data

(62) Division of application No. 09/280,710, filed on Mar. 30, 1999, now Pat. No. 6,150,383, which is a division of application No. 09/057,465, filed on Apr. 9, 1998, now Pat. No. 5,965,584, which is a division of application No. 08/667,979, filed on Jun. 19, 1996, now Pat. No. 5,952,356.

(30) **Foreign Application Priority Data**

Jun. 20, 1995 (JP) 7-153500

(51) **Int. Cl.**[7] **C07D 40/02; A61K 31/44**
(52) **U.S. Cl.** **514/342; 546/269.7**
(58) **Field of Search** 514/342; 546/269.7

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(List continued on next page.)

Primary Examiner—Zinna Northington Davis
(74) *Attorney, Agent, or Firm*—Wenderoth, Lind & Ponack, L.L.P.

(57) **ABSTRACT**

Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with other antidiabetics differing from the enhancer in the mechanism of action, which shows a potent depressive effect on diabetic hyperglycemia and is useful for prophylaxis and treatment of diabetes.

25 Claims, No Drawings

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PHARMACEUTICAL COMPOSITION

This application is a divisional of application Ser. No. 09/280,710, filed Mar. 30, 1999 now U.S. Pat. No. 6,150,383 which is a divisional of Ser. No. 09/057,465, filed Apr. 9, 1998, now U.S. Pat. No. 5,965,584, which is a divisional of application Ser. No. 08/667,979, filed Jun. 19, 1996, now U.S. Pat. No. 5,952,356.

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition comprising an insulin sensitivity enhancer in combination with one or more other antidiabetics differing from said enhancer in the mechanism of action.

Recent years, the pathology of diabetes has become more and more understood and, in parallel, drugs specific for the respective pathologic states have been developed. Accordingly a variety of drugs having new mechanisms of action have appeared one after another.

Insulin sensitivity enhancers are also known as insulin resistance deblockers because they have the action to normalize the impaired insulin receptor function, and are gathering much attention in these years.

Regarding such insulin sensitivity enhancers, a very useful compound such as pioglitazone has been developed [Fujita et al., Diabetes, 32, 804–810, 1983, JP-A S55(1980)-22636 (EP-A 8203), JP-A S61(1986)-267580 (EP-A 193256)]. Pioglitazone restores the impaired insulin receptor function to normalize the uneven distribution of glucose transporters in cells, the cardinal enzyme systems associated with glycometabolism, such as glucokinase, and enzyme systems associated with lipidmetabolism, such as lipoprotein lipase. As the results, insulin resistance are deblocked to improve glucose tolerance, and lower the plasma concentrations of neutral lipids and free fatty acids. Since these actions of pioglitazone are comparatively gradual and the risk of side effect in long-term administration is also low, this compound is useful for obese patients who are presumed to be highly insulin-resistant.

Also, insulin sensitivity enhancers such as CS-045, thazolidinedione derivatives and substituted thiazolidinedione derivatives are reported to be used in combination with insulin [JP-A H4(1992)-66579, JP-A H4(1992)-69383, JP-A H5(1993)-202042]. However, the pharmaceutical composition having a specific combination of the present invention is unknown.

Diabetes is a chronic disease with diverse pathologic manifestations and is accompanied by lipidmetabolism disorders and circulatory disorders as well as glycometabolism disorders. As the results, diabetes tends to progress entailing various complications in many cases. Therefore, it is necessary to select the drug of choice for the prevailing disease state in each individual case. However, this selection is often difficult in clinical settings because single use of each individual drug can not bring sufficient effects in some disease states and there are various problems such as side effect which is caused by an increased dose or a long-term administration.

SUMMARY OF THE INVENTION

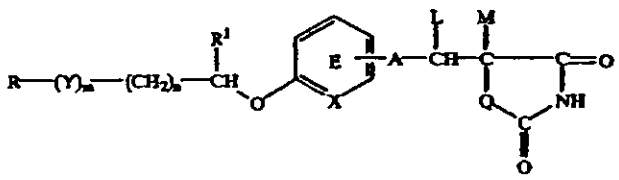
In view of the above state of the art, the inventors of the present invention did much research to develop antidiabetics which would not virtually cause adverse reactions even on long-term administration and could be effective for a large cohort of the diabetic population. As a consequence, they discovered that the above object can be accomplished by using an insulin sensitivity enhancer, such as the drug described above, in combination with other antidiabetics differing from said enhancer in the mechanism of action, and accordingly have perfected the present invention.

The present invention, therefore, relates to:

1) Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with at least one member of the group consisting of an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor;

2) Pharmaceutical composition according to 1), wherein the insulin sensitivity enhancer is a compound represented by the formula:

(I)



wherein R represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR³— (wherein R³ represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R¹ represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 substituents, and the substituents may optionally be combined with R¹ to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; or a pharmacologically acceptable salt thereof;

3) Pharmaceutical composition according to 2), wherein the compound represented by the formula (I) is. pioglitazone;

4) Pharmaceutical composition according to 1), which comprises an insulin sensitivity enhancer in combination with an α-glucosidase inhibitor;

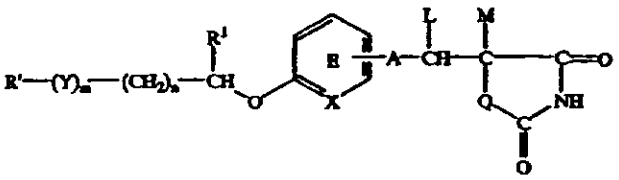
5) Pharmaceutical composition according to 4), wherein the α-glucosidase inhibitor is voglibose;

6) Pharmaceutical composition according to 4), wherein the insulin sensitivity enhancer is pioglitazone and the α-glucosidase inhibitor is voglibose;

7) Pharmaceutical composition according to 1), which is for prophylaxis or treatment of diabetes;

8) Pharmaceutical composition which comprises a compound represented by the formula:

(II)

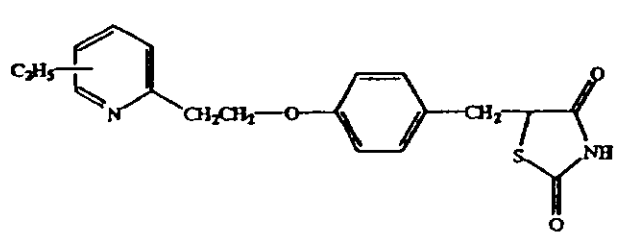


wherein R¹ represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by

—CO—, —CH(OH)— or —NR^3— (wherein R^3 represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R^1 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 substituents, and the substituents may optionally be combined with R^1 to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; with a proviso that R' does not represent benzopyranyl group when m and n are O, X represents CH, A represents a bond, Q represents sulfur atom, R^1, L and M represent hydrogen atom and ring E does not have further substituents; or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation;

9) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is the compound represented by the formula:

(III)



10) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is pioglitazone;

11) Pharmaceutical composition according to 8), wherein the insulin secretion enhancer is glibenclamide;

12) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is pioglitazone and the insulin secretion enhancer is glibenclamide;

13) Pharmaceutical composition according to 8), which is for prophylaxis or treatment of diabetes.

DETAILED DESCRIPTION OF THE INVENTION

The term "insulin sensitivity enhancer" as used in this specification means any and all drug substances that restore the impaired insulin receptor function to deblock insulin resistance and consequently enhance insulin sensitivity. As examples of the insulin sensitivity enhancer, the compound represented by the formula (I) or a pharmacologically acceptable salt thereof can be mentioned.

In the formula (I), as the hydrocarbon group in the optionally substituted hydrocarbon group represented by R, mention is made of aliphatic hydrocarbon groups, alicyclic hydrocarbon groups, alicyclic-aliphatic hydrocarbon groups, aromatic aliphatic hydrocarbon groups and aromatic hydrocarbon groups. Number of carbon atoms in these hydrocarbon groups is preferably 1 to 14.

The aliphatic hydrocarbon groups are preferably those having 1 to 8 carbon atoms. As the aliphatic hydrocarbon groups, mention is made of C_{1-8} saturated aliphatic hydrocarbon groups (e.g. alkyl group) as exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, hexyl, isohexyl, heptyl and octyl, and C_{2-8} unsaturated aliphatic hydrocarbon

groups (e.g. alkenyl group, alkadienyl group, alkynyl group, alkadiynyl group) as exemplified by vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptynyl and 1-octynyl.

The alicyclic hydrocarbon groups are preferably those having 3 to 7 carbon atoms. As the alicyclic hydrocarbon groups, mention is made of C_{3-7} saturated alicyclic hydrocarbon groups (e.g. cycloalkyl group) as exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and C_{5-7} unsaturated alicyclic hydrocarbon groups (e.g. cycloalkenyl group, cycloalkadienyl group) as exemplified by 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl and 2,4-cycloheptadienyl.

As the alicyclic-aliphatic hydrocarbon groups, mention is made of, among those formed by combination of the above-mentioned alicyclic hydrocarbon groups with aliphatic hydrocarbon groups (e.g. cycloalkyl-alkyl group, cycloalkenyl-alkyl group), ones having 4 to 9 carbon atoms as exemplified by cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl and cycloheptylethyl.

The aromatic aliphatic hydrocarbon groups are preferably those having 7 to 13 carbon atoms (e.g. aralkyl group). As the aromatic aliphatic hydrocarbon groups, mention is made of C_{7-9} phenylalkyl as exemplified by benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and 1-phenylpropyl, and C_{11-13} naphthylalkyl as exemplified by α-naphthylmethyl, α-naphthylethyl, β-naphthylmethyl and β-naphthylethyl.

As the aromatic hydrocarbon groups, mention is made of, ones having 6 to 14 carbon atoms as exemplified by phenyl, naphthyl (α-naphtyl, β-naphthyl).

In the formula (I), as the heterocyclic group in the optionally substituted heterocyclic group represented by R, mention is made of, for example, 5- to 7-membered heterocyclic groups containing, as a ring component atom, 1 to 4 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom, and a condensed ring group. As the condensed ring, mention is made of, for example, these 5- to 7-membered heterocyclic groups condensed with 6-membered ring containing one or two nitrogen atoms, benzene ring or 5-membered ring containing one sulfur atom.

Examples of these heterocyclic groups include 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, 1H-indazol-3-yl, 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 1H-imidazo[4,5-b]pyrazin-2-yl and benzopyranyl. Among them, pyridyl, oxazolyl or thiazolyl group is preferable.

In the formula (I), the hydrocarbon group and heterocyclic group represented by R may optionally have 1 to 5, preferably 1 to 3 substituents at any substitutable positions. Examples of such substituents include aliphatic hydrocarbon group, alicyclic hydrocarbon group, aryl group, aromatic heterocyclic group, non-aromatic heterocyclic group, halogen atom, nitro group, optionally substituted amino group, optionally substituted acyl group, optionally substituted hydroxyl group, optionally substituted thiol group, optionally esterified carboxyl group, amidino group, carbamoyl group, sulfamoyl group, sulfo group, cyano group, azido group and nitroso group.

Examples of the aliphatic hydrocarbon groups include C_{1-15} straight-chain or branched aliphatic hydrocarbon groups as exemplified by alkyl group, alkenyl group, and alkynyl group.

Preferable examples of the alkyl group include C_{1-10} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, hexyl, pentyl, octyl, nonyl and decyl.

Preferable examples of the alkenyl group include C_{2-10} alkenyl groups such as vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl.

Preferable examples of the alkynyl group-include C_{2-10} alkynyl groups such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As the alicyclic hydrocarbon group, mention is made of C_{3-12} saturated or unsaturated alicyclic hydrocarbon groups as exemplified by cycloalkyl group, cycloalkenyl group and cycloalkadienyl group.

Preferable examples of cycloalkyl group include C_{3-10} cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl and bicyclo[4.3.1]decyl.

Preferable examples of the cycloalkenyl group include C_{3-10} cycloalkenyl groups such as 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl and 3-cyclohexen-1-yl.

Preferable examples of the cycloalkadienyl group include C_{4-10} cycloalkadienyl groups such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl and 2,5-cyclohexadien-1-yl.

Preferable examples of the aryl group include C_{6-14} aryl groups such as phenyl, naphthyl (1-naphthyl, 2-naphthyl), anthryl, phenanthryl and acenaphthylenyl.

Preferable examples of the aromatic heterocyclic group include aromatic monocyclic heterocyclic groups such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl; and aromatic condensed heterocyclic groups such as benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, 1,2-benzoisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, pinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylidinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenathridinyl, phenathrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl.

Preferable examples of the non-aromatic heterocyclic group include oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidinor piperidino, morpholino and thiomorpholino.

Examples of the halogen atom include fluorine, chlorine, bromine and iodine.

As the substituted amino group in the optionally r substituted amino group, mention is made of, N-monosubstituted amino group and N,N-disubstituted amino group. Examples of the substituted amino groups include amino groups having one or two substituents selected from C_{1-10} alkyl group, C_{2-10} alkenyl group, C_{2-10} alkynyl group, aromatic group, heterocyclic group and C_{1-10} acyl group (e.g. methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclohexylamino, phenylamino, N-methyl-N-phenylamino, acetylamino, propionylamino, benzoylamino and nicotinoylamino).

As the acyl group, mention is made of C_{1-13} acyl groups such as C_{1-10} alkanoyl group, C_{3-10} alkenoyl group, C_{4-10} cycloalkanoyl group, C_{4-10} cycloalkenoyl group and C_{6-12} aromatic carbonyl group.

Preferable examples of the C_{1-10} alkanoyl group include formyl acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl and octanoyl. Preferable examples of the C_{3-10} alkenoyl group include acryloyl, methacryloyl, crotonoyl and isocrotonoyl. Preferable examples of C_{4-10} cycloalkanoyl group include cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl and cycloheptanecarbonyl. Preferable examples of C_{4-10} cycloalkenoyl group include 2-cyclohexenecarbonyl. Preferable examples of C_{6-12} aromatic carbonyl group include benzoyl, naphthoyl and nicotinoyl.

As the substituent in the substituted acyl group, mention is made of, for example, C_{1-3} alkyl group, C_{1-3} alkoxy group, halogen atom (e.g. chlorine, fluorine, bromine, etc.), nitro group, hydroxyl group and amino group.

As the substituted hydroxyl group in the optionally substituted hydroxyl group, mention is made of, for example, alkoxy group, cycloalkyloxy group, alkenyloxy group, cycloalkenyloxy group, aralkyloxy group, acyloxy group and aryloxy group.

Preferable examples of the alkoxy group include C_{1-10} alkoxy groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, t.-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy and nonyloxy. Preferable examples of the cycloalkyloxy group include C_{3-10} cycloalkyloxy groups such as cyclobutoxy, cyclopentyloxy and cyclohexyloxy. Preferable examples of the alkenyloxy group include C_{2-10} alkenyloxy groups such as allyloxy, crotyloxy, 2-pentenyloxy and 3-hexenyloxy. Preferable examples of the cycloalkenyloxy group include C_{3-10} cycloalkenyloxy groups such as

2-cyclopentenyloxy and 2-cyclohexenyloxy. Preferable examples of the aralkyloxy group include C_{7-10} aryloxy groups such as phenyl-C_{1-4}alkyloxy (e.g. benzyloxy and phenethyloxy). Preferable examples of the acyloxy group include C_{2-13} acyloxy group, more preferably C_{2-4} alkanoyloxy groups (e.g. acetyloxy, propionyloxy, butyryloxy and isobutyryloxy). Preferable examples of the aryloxy group include C_{6-14} aryloxy groups such as phenoxy and naphthyloxy. The aryloxy group may optionally have one or two substituents such as halogen atom (e.g. chlorine, fluorine, bromine). Examples of the substituted aryloxy group include 4-chlorophenoxy.

As the substituted thiol group in the optionally substituted thiol group, mention is made of, alkylthio group, cycloalkylthio group, alkenylthio group, cycloalkenylthio group, aralkylthio group, acylthio group and arylthio group.

Preferable examples of thealkylthio group include C_{1-10} alkylthio groups such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec.-butylthio, t.-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio and nonylthio. Preferable examples of the cycloalrylthio group include C3-10 cycloalkylthio groups such as cyclobutylthio, cyclopentylthio and cyclohexylthio. Preferable examples of the alkenylthio group include C_{2-10} alkenylthio groups such as allylthio, crotylthio, 2-pentenylthio and 3-hexenylthio. Preferable examples of the cycloalkenylthio group include C_{3-10} cycloalkenylthio groups such as 2-cyclopentenylthio and 2-cyclohexenyl thio. Preferable examples of the aralkylthio include C_{7-10} aralkylthio groups such as phenyl-C_{1-4}alkylthio (e.g. Benzylthio and phenethyloxy). Preferable examples of the acylthio group include C_{2-13} acylthio group, more preferably C_{2-4} alkanoyl thio groups (e.g. Acetylthio, propionyl thio, butyryl thio and isobutyryl thio).

Preferable examples of the arylthio group include C_{6-14} arylthio groups such as phenylthio and naphthylthio. The arylthio group may optionally have one or two substituents such as halogen atom (e.g. Chlorine, fluorine, bromine). Examples of the substituted arylthio group include 4-chlorophenyl thio.

As the optionally esterified carboxyl group, mention is made of, for example, alkoxycarbonyl group, aralkyloxycarbonyl group and aryloxycarbonyl group.

Preferable examples of the alkoxycarbonyl group include C_{2-5} alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and butoxycarbonyl. Preferable examples of the aralkyloxycarbonyl group include C_{8-10} aralkyloxycarbonyl groups such as benzyloxycarbonyl. Preferable examples of the aryloxycarbonyl group include C_{7-15} aryloxycarbonyl groups such as phenoxycarbonyl and p-tolyloxycarbonyl.

Among the substituents on the hydrocarbon group and heterocyclic group represented by R, C_{1-10} alkyl groups, aromatic heterocyclic groups and C_{6-14} aryl groups are preferable, and C_{1-3} alkyl, furyl, thienyl, phenyl and naphthyl are especially preferable.

In the formula (I), substituents on the hydrocarbon group and heterocyclic group which are represented by R, may, when they are alicyclic hydrocarbon group, aryl group, aromatic heterocyclic group or non-aromatic heterocyclic group, have one or more, preferably 1 to 3, of suitable substituents respectively. Examples of these substituents include C_{1-6} alkyl groups, C_{2-6} alkenyl groups, C_{2-6} alkynyl groups, C_{3-7} cycloalkyl groups, C_{6-14} aryl groups, aromatic heterocyclic groups (e.g. thienyl, furyl, pyridyl, oxazolyl and thiazolyl), non-aromatic heterocyclic groups (e.g. tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolidino and piperazino), C_{7-9} aralkyl groups, amino group, N-mono-C_{1-4} alkylamino groups, N,N-di-C_{1-4} alkylamino groups, C_{2-8} acylamino groups (e.g. acetylamino, propionylamino and benzoylamino), amidino group, C_{2-8} acyl group (e.g. C_{2-8} alkanoyl groups), carbamoyl group, N-mono-C_{1-4} alkyl carbamoyl groups, N,N-di-C_{1-4} alkyl carbamoyl groups, sulfamoyl group, N-mono-C_{1-4} alkyl sulfamoyl groups, N,N-di-C_{1-4} alkyl sulfamoyl groups, carboxyl group, C_{2-8} alkoxycarbonyl groups, hydroxyl group, C_{1-4} alkoxy groups, C_{2-5} alkenyloxy groups, C_{3-7} cycloalkyloxy groups, C_{7-9} aralkyloxy groups, C_{6-14} aryloxy groups, mercapto group, C_{1-4} alkylthio groups, C_{7-9} aralkylthio groups C_{6-14} arylthio groups, sulfo group, cyano group, azido group, nitro group, nitroso group and halogen atom.

In the formula (I), R is preferably an optionally substituted heterocyclic group. R is more preferably pyridyl, oxazolyl or thiazolyl group which is optionally substituted by 1 to 3 substituents selected from C_{1-3} alkyl group, furyl group, thienyl group, phenyl group and naphthyl group.

R' in the formula (II) has the same definition as R except that R' does not represent benzopyranyl group when m and n are 0; X represents CH; A represents a bond; Q represents sulfur atom; R^1, L and M represent hydrogen atom; and ring E does not have further substituents.

In the formulae (I) and (II), Y represents —CO—, —CH(OH)— or —NR— (wherein R^3 represents an optionally substituted alkyl group), preferably —CH(OH)— or —NR^3—. As the alkyl group in the optionally substituted alkyl group represented by R^3, mention is made of, for example, C_{1-4} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl and t.-butyl. Examples of the substituents include halogen (e.g., fluorine, chlorine, bromine and iodine), C_{1-4} alkoxy groups (e.g. methoxy, ethoxy, propoxy, butoxy, isobutoxy, sec.-butoxy and t.-butoxy), hydroxyl group, nitro group and C_{1-4} acyl groups (e.g. formyl, acetyl and propionyl).

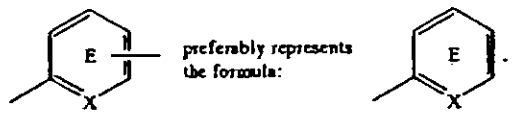
The symbol m is 0 or 1, preferably 0.

The symbol n is 0, 1 or 2, preferably 0 or 1.

X represents CH or N, preferably CH.

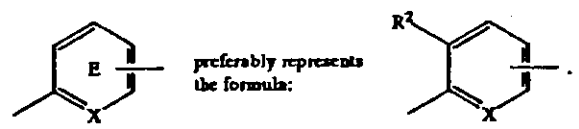
In the formulae (I) and (II), A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group. The aliphatic hydrocarbon group may be straight-chain or branched, and saturated or unsaturated. Specific examples of the aliphatic hydrocarbon group include saturated ones [e.g. —CH_2—, —$CH(CH_3)$—, —$(CH_2)_2$—, —$CH(C_2H_5)$—, —$(CH_2)_3$—, —$(CH_2)_4$—, —$(CH_2)_5$—, —$(CH_2)_6$— and —$(CH_2)_7$—] and unsaturated ones [e.g. —CH=CH—, —$C(CH_3)$=CH—, —CH=CH—CH_2—, —$C(C_2H5)$=CH—, —CH_2—CH=CH—CH_2—, —CH_2—CH_2—CH=CH—CH_2—. —CH=CH—CH=CH—CH_2— and —CH=CH—CH=CH—CH=CH—CH_2—. A is preferably a bond or C_{1-4} divalent aliphatic hydrocarbon groups, the aliphatic hydrocarbon groups preferably being saturated. A is more preferably a bond or —$(CH_2)_2$—. As the alkyl group represented by R^1, substantially the same one as the alkyl group in the above-mentioned R^3. R^1 is preferably hydrogen atom.

In the formulae (I) and (II), the partial formula:



Ring E has 1 to 4 substituents at any substitutable positions. Examples of such substituents include alkyl group, optionally substituted hydroxyl group, halogen atom, optionally substituted acyl group and optionally substituted amino group. These substituents have substantially the same meaning as those described as substituents of the hydrocarbon group and heterocyclic group represented by R.

Ring E, namely the partial formula:



wherein R^2 represents hydrogen atom, an alkyl group, an optionally substituted hydroxyl group, a halogen atom, an optionally substituted acyl group, nitro group or an optionally substituted amino group.

As the alkyl group, optionally substituted hydroxyl group, halogen atom, optionally substituted acyl group and optionally substituted amino group represented by R^2, mention is made of those described as substituents of the hydrocarbon group and heterocyclic group represented by R. R^2 is preferably hydrogen atom, optionally substituted hydroxyl group or halogen atom, more preferably hydrogen atom or optionally substituted hydroxyl group, especially preferably hydrogen atom or C_{1-4} alkoxy groups.

In the formulae (I) and (II), L and M represent hydrogen atom, or they may optionally be combined with each other to form a bond. L and M are preferably hydrogen atom.

In the compounds wherein L and M are combined with each other to form a bond, there exist (E)- and (Z)-isomers relative to the double bond at the 5-position of the azolidinedione ring.

And, in the compounds wherein L and M respectively represent hydrogen atom, there exist (R)- and (S)-optical isomers due to the asymmetric carbon at the 5-position of the azolidinedione ring. The compounds include these (R)- and (S)-optical isomers and racemic isomers.

Preferable examples of the compounds represented by the formula (I) or (II) includes those in which R is pyridyl, oxazolyl or thiazolyl group optionally having 1 to 3 substituents selected from C_{1-3} alkyl, furyl, thienyl, phenyl and naphthyl; m is 0; n is 0 or 1; X is CH; A is a bond or $-(CH_2)_2-$; R^1 is hydrogen atom; ring E, namely the partial formula:

and R^2 is hydrogen atom or C_{1-4} alkoxy group; and L and M are both hydrogen atom.

Preferable examples of the compound represented by the formula (I) include

(1) the compound represented by the formula (III) such as 5-[4-[2-(3-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione; 5-[4-[2-(4-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione; 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (generic name: pioglitazone); and 5-[4-[2-(6-ethyl-2-pyridyl)-ethoxy]benzyl]-2,4-thiazolidinedione;

(2) (R)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione; and

(3) 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (generic name: troglitazone/CS-045).

The compound represented by the formula (I) is especially preferably pioglitazone.

The compound represented by the formula (II) is preferably the compound represented by the formula (III) and (R)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione, more preferably pioglitazone.

The pharmacologically acceptable salt of the compound represented by the formula (I) or (II) are exemplified by salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

Preferable examples of salts with inorganic bases include salts with alkali metals such as sodium, potassium, etc., salts with alkaline earth metals such as calcium, magnesium, etc., and salts with aluminum, ammonium, etc.

Preferable examples of salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, etc.

Preferable examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.

Preferable examples of salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acids benzenesulfonic acid, p-toluenesulfonic acid, etc.

Preferable examples of salts with basic amino acids include salts with arginine, lysine, ornithine, etc., and preferable examples of salts with acidic amino acids include salts with aspartic acid, glutamic acid, etc.

The pharmacologically acceptable salt of the compound represented by the formula (III) is preferably a salt with an inorganic acid, more preferably a salt with hydrochloric acid. Especially, pioglitazone is preferably used in the form of salt with hydrochloric acid.

The compounds represented by the formula (I) or (II) or a salt thereof can be produced in accordance with, for example, methods described in JPA S55(1980)-22636(EP-A 8203), JPA S60(1985)-208980(EP-A 155845), JPA S61(1986)-286376(EP-A 208420), JPA S61(1986)-85372(EP-A 177353), JPA S61(1986)-267580(EP-A 193256), JPA H5(1993)-86057(WO 92/18501), JPA H7(1995)-82269 (EP-A 605228), JPA H7(1995)-101945(EP-A 612743), EP-A 643050, EP-A 710659, etc. or methods analogous thereto.

Insulin sensitivity enhancers include 5-[(3,4-dihydro-2-(phenylmethyl)-2H-1-benzopyran-6-yl]methyl]-2,4-thiazolidinedione (generic name: englitazone) or its sodium salt;

5-[[4-[3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl]phenyl]methyl]-2,4-thiazolidinedione (generic name: darglitazone/CP-86325) or its sodium salt;

5-[2-(5-methyl-2-phenyl-4-oxazolylmethyl)benzofuran-5-ylmethyl]-2,4-oxazolidinedione (CP-92768); a5-(2-naphthalenylsulfonyl)-2,4-thiazolidinedione (AY-31637);

4-[(2-naphthalenyl)methyl]-3H-1,2,3,5-oxathiadiazol-2-oxide (AY-30711); and

5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]-methyl], 2,4-thiazolidinedione (BRL-49653), etc. in addition to compounds mentioned hereinbefore.

In the present invention, examples of the drug which is used in combination with the above-mentioned insulin sensitivity enhancer include an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor. α-Glucosidase inhibitors are drugs which inhibit digestive enzymes such as amylase, maltase, α-dextrinase, sucrase, etc. to retard digestion of starch and sugars. Examples of the α-glucosidase inhibitors include acarbose, N-(1,3-dihydroxy-2-propyl)valiolamine (generic name; voglibose), miglitol, etc. with preference given to voglibose.

Aldose reductase inhibitors are drugs which inhibit the first-stage rate-limiting enzyme in the polyol pathway to prevent or arrest diabetic complications. In the hyperglycemic state of diabetes, the utilization of glucose in the polyol pathway is increased and the excess sorbitol accumulated intracellularly as a consequence acts as a tissue toxin and hence evokes the onset of complications such as diabetic neuropathy, retinopathy, and nephropathy. Examples of the aldose reductase inhibitors include tolurestat; epalrestat; 3,4-dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxazine-4-acetic acid; 2,7-difluoro-spiro(9H-fluorene-9,4'-imidazolidine)-2',5'-dione (generic name: imirestat); 3-[(4-bromo-2-fluorophenyl) methyl]-7-chloro-3,4-dihydro-2,4-dioxo-1(2H)-quinazoline acetic acid (generic name: zenarestat); 6-fluoro-2,3-dihydro-2',5'-dioxo-spiro[4H-1-benzopyran-4,4'-imidazolidine]-2-carboxamide (SNK-860); zopolrestat; sorbinil; and 1-[(3-bromo-2-benzofuranyl) sulfonyl]-2,4-imidazolidinedione (M-16209), etc.

Biguanides are drugs having actions of stimulation of anaerobic glycolysis, increase of the sensitivity to insulin in the peripheral tissues, inhibition of glucose absorption from the intestine, suppression of hepatic gluconeogenesis, and inhibition of fatty acid oxidation. Examples of the biguanides include phenformin, metformin, buformin etc.

Statin compounds are drugs having actions of lowering blood cholesterol levels by inhibiting hydroxymethylglutalyl CoA (HMG-CoA) reductase. Examples of the statin compounds include pravastatin and its sodium salt, simvastatin, lovastatin, atorvastatin, fluvastatin, etc.

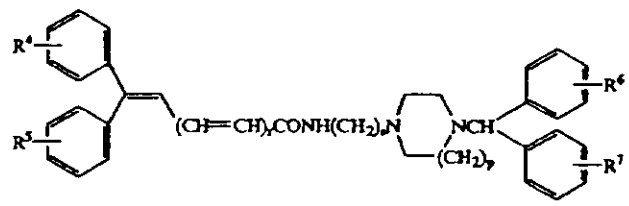
Squalene synthesis inhibitors are drugs having actions of lowering blood cholesterol levels by inhibiting synthesis of squalene. Examples of the squalene synthesis inhibitors include (S)-α-[Bis[2,2-dimethyl-1-oxopropoxy)methoxy] phosphinyl]-3-phenoxybenzenebutanesulfonic acid, mono potassium salt (BMS-188494).

Fibrate compounds are drugs having actions of lowering blood cholesterol levels by inhibiting synthesis and secretion of triglycerides in liver and activating a lipoprotein lipase.

Examples of the fibrate compounds include bezafibrate, beclobrate, binifibrate, ciplofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate, etc.

LDL catabolism enhancers are drugs having actions of lowering blood cholesterol levels by increasing-the number of LDL (low-density lipoprotein) receptors.

Examples of the LDL catabolism enhancers include the compound which is described in JPA H7(1995)-316144 and represented by the formula:



wherein R^4, R^5, R^6 and R^7 are the same or different, and represent hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group; r is 0–2; s is 2–4; p is 1–2; or a salt thereof; specifically N-[2-[4-bis(4-fluorophenyl) methyl-1-piperazinyl]ethyl]-7, 7-diphenyl-2,4,6-heptatrienic acid amide, etc.

The above-mentioned statin compounds, squalene synthesis inhibitors, fibrate compounds and LDL catabolism enhancers can be substituted with other drugs having the property to lower blood cholesterol and triglyceride levels. Examples of these drugs include nicotinic acid derivatives such as nicomol and niceritrol; antioxidants such as probucol; and ion-exchange resins such as colestyramin.

Angiotensin converting enzyme inhibitors are drugs having actions of partially lowering blood glucose levels as well as lowering blood pressure by inhibiting angiotensin converting enzymes. Examples of the angiotensin converting enzyme inhibitors include captopril, enalapril, alacepril, delapril, ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moveltopril, perindopril, quinapril, spirapril, temocapril, trandolapril, etc.

In the present invention, especially preferred is the pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with an α-glucosidase inhibitor. The insulin sensitivity enhancer is especially preferably pioglitazone, and the α-glucosidase inhibitor is especially preferably voglibose.

In the present invention, examples of the drug which is used in combination with the compound represented by the formula (II) or a pharmacologically acceptable salt thereof include an insulin secretion enhancer and/or an insulin preparation.

Insulin secretion enhancers are drugs having the property to promote secretion of insulin from pancreatic β cells. Examples of the insulin secretion enhancers include sulfonylureas (SU). The sulfonylureas (SU) are drugs which promote secretion of insulin from pancreatic β cells by transmitting signals of insulin secretion via SU receptors in the cell membranes. Examples of the SU include-tolbutamide; chlorpropamide; tolazamide; acetohexamide; 4-chloro-N-[(1-pyrolidinylamino)carbonyl]-benzenesulfonamide (generic name: glycopyramide) or its ammonium salt; glibenclamide (glyburide); gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibornuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; tolcyclamide, etc.

Insulin secretion enhancers include N-[[4-(1-methylethyl) cyclohexyl)carbonyl]-D-phenylalanine (AY-4166); calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl) propionate dihydrate KAD-1229); and glimepiride (Hoe 490), etc. in addition to compounds mentioned hereinbefore. The insulin secretion enhancer is especially preferably glibenclamide.

Examples of the insulin preparations include animal insulin preparations typically extracted from bovine or porcine pancreas and human insulin, preparations synthesized by genetic engineering techniques typically using *Escherichia*

coli or yeasts. While insulin preparations are available in a variety of types, e.g. immediate-acting, bimodal-acting, intermediate-acting, and long-acting, these types of preparations can be selectively administered according to the patient's condition.

In the present invention, especially preferred is the pharmaceutical composition which comprises the compound represented by the formula (II) or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer. The compound represented by the formula (II) or a pharmacologically acceptable salt thereof is especially preferably pioglitazone, and the insulin secretion enhancer is especially preferably glibenclamide.

The pharmaceutical composition comprising an insulin sensitivity enhancer in combination with at least one member selected from the group consisting of an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor; and the pharmaceutical composition comprising the compound represented by the formula (II) or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation, both provided in accordance with the present invention, can be respectively put to use by mixing the respective active components either all together or independently with a physiologically acceptable carrier, excipient, binder, diluent, etc. and administering the mixture or mixtures either orally or non-orally as a pharmaceutical composition. When the active components are formulated independently, the respective formulations can be extemporaneously admixed using a diluent or the like and administered or can be administered independently of each other, either concurrently or at staggered times to the same subject.

The dosage form for said pharmaceutical composition includes such oral dosage forms as granules, powders, tablets, capsules, syrups, emulsions, suspensions, etc. and such non-oral dosage forms as injections (e.g. subcutaneous, intravenous, intramuscular and intraperitoneal injections), drip infusions, external application forms (e.g. nasal spray preparations, transdermal preparations, ointments, etc.), and suppositories (e.g. rectal and vaginal suppositories).

These dosage forms can be manufactured by the per se known technique conventionally used in pharmaceutical procedures. The specific manufacturing procedures are as follows.

To manufacture an oral dosage form, an excipient (e.g. lactose, sucrose, starch, mannitol, etc.), a dis-integrator (e.g. calcium carbonate, carboxymethylcellulose calcium, etc.), a binder (e.g. α-starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, etc.), and a lubricant (e.g. talc, magnesium stearate, polyethylene glycol 6000, etc.), for instance, are added to the active component or components and the resulting composition is compressed. Where necessary, the compressed product is coated, by the per se known technique, for masking the taste or for enteric dissolution or sustained release. The coating material that can be used includes, for instance, ethyl-cellulose, hydroxymethylcellulose, polyoxyethylene glycol, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, and Eudragit (Rohm & Haas, Germany, methacrylic-acrylic copolymer).

Injections can be manufactured typically by the following procedure. The active component or components are dissolved, suspended or emulsified in in aqueous vehicle (e.g. distilled water, physiological saline., Ringer's solution, etc.) or an oily vehicle (e.g. vegetable oil such as olive oil, sesame oil; cottonseed oil, corn oil, etc. orpropylene glycol) together with a dispersant (e.g. Tween 80 (Atlas Powder, U.S.A.), HCO 60 (Nikko Chemicals), polyethylene glycol, carboxymethylcellulose, sodium alginate, etc.), a preservative (e.g. methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, benzyl alcohol, chlorobutanol, phenol, etc.), an isotonizing agent (e.g. sodium chloride, glycerol, sorbitol, glucose, inverted sugar, etc.) and other additives. If desired, a solubilizer (e.g. sodium salicylate, sodium acetate, etc.), a stabilizer (e.g. human serum albumin), a soothing agent (e.g. benzalkonium chloride, procaine hydrochloride, etc.) and other additives can also be added.

A dosage form for external application can be manufactured by processing the active component or components into a solid, semi-solid or liquid composition. To manufacture a solid composition, for instance, the active component or components, either as they are or in admixture with an excipient (e.g. lactose, mannitol, starch, microcrystalline cellulose, sucrose, etc.), a thickener (e.g. natural gums, cellulose derivatives, acrylic polymers, etc.), etc., are processed into powders. The liquid composition can be manufactured in substantially the same manner as the injections mentioned above. The semi-solid composition is preferably provided in a hydrous or oily gel form or an ointment form. These compositions may optionally contain a pH control agent (e.g. carbonic acid, phosphoric acid, citric acid, hydrochloric acid, sodium hydroxide, etc.), and a preservative (e.g. p-hydroxybenzoic acid esters, chlorobutanol, benzalkonium chloride, etc.), among other additives.

Suppositories can be manufactured by processing the active component or components into an oily or aqueous composition, whether solid, semi-solid or liquid. The oleaginous base that can be used includes, for instance, higher fatty acid glycerides [e.g. cacao butter, Witepsols (Dinamit-Nobel), etc.], medium-chain fatty acids [e.g. Migriols (Dinamit-Nobel), etc.], vegetable oils (e.g. sesame oil, soybean oil, cotton-seed oil, etc.), etc. The water-soluble base includes, for instance, polyethylene glycols, propylene glycol, etc. The hydrophilic base includes, for instance, natural gums, cellulose derivatives, vinyl polymers, and acrylic polymers, etc.

The pharmaceutical composition of the present invention is low in toxicity and can be safely used in mammals (e.g. humans, mice, rats, rabbits, dogs, cats, bovines, horses, swines, monkeys).

The dosage of the pharmaceutical composition of the present invention may be appropriately determined with reference to the dosages recommended for the respective active components and can be selected appropriately according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of the active components, among other factors. For example, the dosage of the insulin sensitivity enhancer for an adult can be selected from the clinical oral dose range of 0.01 to 10 mg/kg body weight (preferably 0.05 to 10 mg/kg body weight, more preferably 0.05 to 5 mg/kg body weight) or the clinical parenteral dose range of 0.005 to 10 mg/kg body weight (preferably 0.01 to 10 mg/kg body weight, more preferably 0.01 to 1 mg/kg body weight). The other active component or components having different modes of action for use in combination can also be used in dose ranges selected by referring to the respective recommended clinical dose ranges. The preferred frequency of administration is 1 to 3 times a day.

The proportions of the active components in the pharmaceutical composition of the present invention can be appro-

priately selected according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of active components, among other factors. When, for example, the compound represented by the formula (I) or a pharmacologically acceptable salt thereof (e.g. pioglitazone) which is the insulin sensitivity enhancer and voglibose which is an α-glucosidase inhibitor are to be administered in combination to a human subject, voglibose is used in a proportion of usually about 0.000 to 0.2 weight parts and preferably about 0.001 to 0.02 weight parts relative to 1 weight part of the compound or a salt thereof. When, for example, the compound represented by the formula (II) or a pharmacologically acceptable salt thereof and glibenclamide which is an insulin secretion enhancer are to be administered in combination to a human subject, glibenclamide is used in a proportion of usually about 0.002 to 5 weight parts and preferably about 0.025 to 0.5 weight parts, relative to 1 weight-part of the compound or a pharmacologically acceptable salt thereof.

The pharmaceutical composition of the present invention shows a marked synergistic effect compared with administration of either active component alone. For example, compared with cases in which each of these active components was administered to diabetic Wistar fatty rats with genetical obsesity, administration of these active components in combination resulted in marked improvements in both hyperglycemia and reduced glucose tolerance. Thus, the pharmaceutical composition of the present invention lowers blood glucose in diabetics more effectively than it is the case with administration of each component drug alone and, therefore, can be used advantageously for the prophylaxis and treatment of diabetic complications.

Furthermore, since the pharmaceutical composition of the present invention develops sufficient efficacy with reduced doses as compared with the administration of any one of the active components alone, the side effects of the respective components (e.g. gastrointestinal disorders such as diarrhea, etc.) can be reduced.

The following working examples and experimental examples are merely intended to illustrate the present invention in further detail but should by no means be construed as defining the scope of the invention.

The pharmaceutical composition of the present invention can be prepared according to the following formulations.

WORKING EXAMPLE 1

Capsules	
(1) Pioglitazone hydrochloride	30 mg
(2) Voglibose	0.2 mg
(3) Lactose	60 mg
(4) Microcrystalline cellulose	79.8 mg
(5) Magnesium stearate	10 mg
Total	180 mg

The whole amounts of (1), (2), (3) and (4) and half the amount of (5) are mixed well and granulated in the conventional manner. Then, the balance of (5) is added and, after mixing, the whole composition is filled in a gelatin hard capsule shell.

WORKING EXAMPLE 2

Tablets	
(1) Pioglitazone hydrochloride	10 mg
(2) Glibenclamide	1.25 mg
(3) Lactose	86.25 mg
(4) Corn starch	20 mg
(5) Polyethylene glycol	2.5 mg
(6) Hydroxypropylcellulose	4 mg
(7) Carmellose calcium	5.5 mg
(8) Magnesium stearate	0.5 mg
	130 mg (per tablet)

The whole amounts of (1), (2), (3), (4), and (5), ⅔ amounts of (6) and (7), and ½ amount of (8) are mixed well and granulated in the conventional manner. Then, the balances of (6), (7) and (8) are added to the granules, which is mixed well and the whole composition is compressed with a tablet machine. The adult dosage is 3 tablets/day, to be taken in 1 to 3 divided doses.

WORKING EXAMPLE 3

Capsules	
(1) Pioglitazone hydrochloride	10 mg
(2) Epalrestat	50 mg
(3) Lactose	55 mg
(4) Microcrystalline cellulose	55 mg
(5) Magnesium stearate	10 mg
Total	180 mg

The whole amounts of (1), (2), (3) and (4) and ½ amount of (5) are mixed well and granulated in the conventional manner. Then, the balance of (5) is added and the whole composition is filled in gelatin capsule, shell. The adult dosage is 3 capsules/day, to be taken in 1 to 3 divided doses.

EXPERIMENTAL EXAMPLE 1

Effect of pioglitazone hydrochloride in combination with α-glucosidase inhibitor in genetically obese and diabetic Wistar fatty rats

Male Wistar fatty rats aged 14–19 weeks were divided into 4 groups of 5–6, and pioglitazone hydrochloride (1 mg/kg body wt./day, p.o.) and/or voglibose (an α-glucosidase inhibitor) (0.31 mg/kg body wt./day; administered by mixing in commercial diet at a rate of 5 ppm) was administered for 14 days. The blood was then collected from the tail vein and the plasma glucose and hemoglobin A_1 were determined by the enzymatic method (Encore Chemical System, Baker) and using a commercial kit (NC-ROPET, Nippon Chemiphar Co.), respectively. The results were expressed in mean± standard deviation for each group (n=5–6) and analyzed by Dunnett's test, which are shown in Table 1. The 1% level of significance was used.

TABLE 1

Group	Plasma glucose (mg/dl)	Hemoglobin A_1 (%)
Control	345 ± 29	5.7 ± 0.4
Pioglitazone	215 ± 50*	5.2 ± 0.3
Voglibose	326 ± 46	6.0 ± 0.6
Pioglitazone + voglibose	114 ± 23*	4.5 ± 0.4*

*P < 0.01 vs. control group

It is apparent from Table 1 that both the blood glucose and hemoglobin A_1 levels were remarkably lowered by combined administration of pioglitazone and voglibose as compared with the administration of either drug alone.

EXPERIMENTAL EXAMPLE 2

Effect of pioglitazone hydrochloride in combination with an insulin secretion enhancer in genetically obese arid diabetic Wistar fatty rats Male Wistar fatty rats aged 13–14 weeks were divided into 4 groups of 5, and pioglitazone hydrochloride (3 mg/kg/day, p.o.) and/or glibenclamide (an insulin secretion enhancer) (3 mg/kg/day, p.o.) was administered for 7 days. Following an overnight fast, the oral glucose,loading test (2 g glucose/kg/5 ml, p.o.) was carried out. Prior to glucose loading and 120 and 240 minutes after the loading, blood was collected from the tail vein and the plasma glucose was assayed by the enzymatic method (Encore Chemical System, Baker). The results were expressed in mean±SD for each group (n=5) and analyzed by Dunnett's test, which are shown in Table 2.

TABLE 2

Group	Plasma glucose (mg/dl) 0 min.	120 min.	240 min.
Control	119 ± 9	241 ± 58	137 ± 10
Pioglitazone	102 ± 12	136 ± 17*	102 ± 9*
Glibenclamide	118 ± 12	222 ± 61	106 ± 24*
Pioglitazone + glibenclamide	108 ± 3	86 ± 10*	60 ± 5*

*P < 0.01 vs. control group

It is apparent from Table 2 that the increase of blood sugar following glucose loading was remarkably inhibited by the combined administration of pioglitazone and glibenclamide as compared with the administration of either drug alone.

The pharmaceutical composition of the present invention shows a potent depressive effect on diabetic hyperglycemia and is useful for prophylaxis and treatment of diabetes. Moreover, this pharmaceutical composition is useful for prophylaxis and treatment of diabetic complications such as diabetic neuropathy, nephropathy, retinopathy, macroangiopathy, and osteopenia. In addition, by appropriately selecting the kinds of component drugs, administration route, dosage, etc. according to clinical status, stable. hypoglycemic efficacy in long-term therapy can be expected with an extremely low risk of side effect.

What is claimed is:

1. A pharmaceutical composition comprising an insulin sensitivity enhancer in combination with an insulin secretion enhancer, wherein the insulin sensitivity enhancer is selected from the group consisting of:

(1) 5-(4-(2-(3-ethyl-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione or its pharmacologically acceptable salt,

(2) 5-(4-(2-(4-ethyl-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione or its pharmacologically acceptable salt,

(3) 5-(4-(2-(5-ethyl-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione or its pharmacologically acceptable salt, and

(4) 5-(4-(2-(6-ethyl-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione or its pharmacologically acceptable salt.

2. The pharmaceutical composition according to claim 1, wherein the insulin sensitivity enhancer is pioglitazone or its hydrochloride.

3. The pharmaceutical composition according to claim 1, wherein the insulin secretion enhancer is a sulfonylurea.

4. The pharmaceutical composition according to claim 3, wherein the sulfonylurea is selected from tolbutamide, chlorpropamide, tolazamide, acetohexamide, 4-chloro-N-[(1-pyrolidinylamino)carbonyl]-benzenesulfonamide or its ammonium salt, glibenclamide, gliclazide, 1-butyl-3-metanilylurea, carbutamide, glibonuride, glipizide, gliquidone, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide and tolcyclamide.

5. The pharmaceutical composition according to claim 1, wherein the insulin secretion enhancer is glibenclamide.

6. The pharmaceutical composition according to claim 1, wherein the insulin sensitivity enhancer is pioglitazone or its hydrochloride and the insulin secretion enhancer is glibenclamide.

7. The pharmaceutical composition according to claim 1, which is for the treatment of diabetes.

8. The pharmaceutical composition according to claim 1, wherein the amount of the insulin secretion enhancer is about 0.002 to 5 weight parts relative to one weight part of the insulin sensitivity enhancer.

9. The pharmaceutical composition according to claim 1, wherein the amount of the insulin secretion enhancer is about 0.025 to 0.5 weight parts relative to one weight part of the insulin sensitivity enhancer.

10. The pharmaceutical composition according to claim 1, which has a synergistic effect for the treatment of diabetes in humans.

11. The pharmaceutical composition according to claim 8, which has a synergistic effect for the treatment of diabetes in humans.

12. The pharmaceutical composition according to claim 9, which has a synergistic effect for the treatment of diabetes in humans.

13. A method for treating diabetes in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of an insulin sensitivity enhancer in combination with an insulin secretion enhancer, wherein the insulin sensitivity enhancer is selected from the group consisting of:

(1) 5-(4-(2-(3-ethyl-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione or its pharmacologically acceptable salt,

(2) 5-(4-(2-(4-ethyl-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione or its pharmacologically acceptable salt,

(3) 5-(4-(2-(5-ethyl-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione or its pharmacologically acceptable salt,

(4) 5-(4-(2-(6-ethyl-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione or its pharmacologically acceptable salt.

14. The method according to claim 13, wherein the insulin sensitivity enhancer is pioglitazone or its hydrochloride.

15. The method according to claim 13, wherein the insulin secretion enhancer is a sulfonylurea.

16. The method according to claim 15, wherein the sulfonylurea is selected from tolbutamide, chlorpropamide, tolazamide, acetohexamide, 4-chloro-N-[(1-pyrolidinylamino)carbonyl]-benzenesulfonamide or its ammonium salt, glibenclamide, gliclazide, 1-butyl-3-metanilylurea, carbutamide, glibonuride, glipizide, gliquidone, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide and tolcyclamide.

17. The method according to claim 13, wherein the insulin secretion enhancer is glibenclamide.

18. The method according to claim 13, wherein the insulin sensitivity enhancer is pioglitazone or its hydrochloride and the insulin secretion enhancer is glibenclamide.

19. The method according to claim 13, wherein the amount of the insulin secretion enhancer is about 0.002 to 5 weight parts relative to one weight part of the insulin sensitivity enhancer.

20. The method according to claim 13, wherein the amount of the insulin secretion enhancer is about 0.025 to 0.5 weight parts relative to one weight part of the insulin sensitivity enhancer.

21. The method according to claim 13, which provides a synergistic effect for the treatment of diabetes in humans.

22. The method according to claim 19, which provides a synergistic effect for the treatment of diabetes in humans.

23. The method according to claim 20, which provides a synergistic effect for the treatment of diabetes in humans.

24. The method according to claim 13, wherein the insulin sensitivity enhancer and the insulin secretion enhancer are mixed together to form an admixture and the admixture is administered to the mammal.

25. The method according to claim 13, wherein the insulin sensitivity enhancer and the insulin secretion enhancer are not mixed together to form an admixture but are administered independently to the mammal.

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US006150383A

United States Patent [19]

Ikeda et al.

[11] Patent Number: 6,150,383

[45] Date of Patent: Nov. 21, 2000

[54] PHARMACEUTICAL COMPOSITION

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[21] Appl. No.: 09/280,710

[22] Filed: Mar. 30, 1999

Related U.S. Application Data

[62] Division of application No. 09/057,465, Apr. 9, 1998, Pat. No. 5,965,584, which is a division of application No. 08/667,979, Jun. 19, 1996, Pat. No. 5,952,356.

[30] Foreign Application Priority Data

Jun. 20, 1995 [JP] Japan 7-153500

[51] Int. Cl.[7] C07D 401/02; A61K 31/44; A61K 31/425; A61K 31/42

[52] U.S. Cl. 514/342; 514/340; 514/369; 514/376; 546/269.7; 546/271.4; 548/183; 548/227

[58] Field of Search 514/340, 342, 514/369, 376; 546/269.7, 271.4; 548/183, 227

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[57] ABSTRACT

Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with other antidiabetics differing from the enhancer in the mechanism of action, which shows a potent depressive effect on diabetic hyperglycemia and is useful for prophylaxis and treatment of diabetes.

18 Claims, No Drawings

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PHARMACEUTICAL COMPOSITION

This application is a divisional of application Ser. No. 09/057,465, filed Apr. 9, 1998, now U.S. Pat. No. 5,965,584 which is a divisional of application Ser. No. 08/667,979, filed Jun. 19, 1996, now U.S. Pat. No. 5,952,356.

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition comprising an insulin sensitivity enhancer in combination with one or more other antidiabetics differing from said enhancer in the mechanism of action.

BACKGROUND OF THE INVENTION

Recent years, the pathology of diabetes has become more and more understood and, in parallel, drugs specific for the respective pathologic states have been developed. Accordingly a variety of drugs having new mechanisms of action have appeared one after another.

Insulin sensitivity enhancers are also known as insulin resistance deblockers because they have the action to normalize the impaired insulin receptor function, and are gathering much attention in these years.

Regarding such insulin sensitivity enhancers, a very useful compound such as pioglitazone has been developed [Fujita et al., Diabetes, 32, 804–810, 1983, JP-A S55(1980)-22636 (EP-A 8203), JP-A S61(1986)-267580 (EP-A 193256)]. Pioglitazone restores the impaired insulin receptor function to normalize the uneven distribution of glucose transporters in cells, the cardinal enzyme systems associated with glycometabolism, such as glucokinase, and enzyme systems associated with lipidmetabolism, such as lipoprotein lipase. As the results, insulin resistance are deblocked to improve glucose tolerance, and lower the plasma concentrations of neutral lipids and free fatty acids. Since these actions of pioglitazone are comparatively gradual and the risk of side effect in long-term administration is also low, this compound is useful for obese patients who are presumed to be highly insulin-resistant.

Also, insulin sensitivity enhancers such as CS-045, thazolidinedione derivatives and substituted thiazolidinedione derivatives are reported to be used in combination with insulin [JP-A H4(1992)-66579, JP-A H4(1992)-69383, JP-A H5(1993)-202042]. However, the pharmaceutical composition having a specific combination of the present invention is unknown.

Diabetes is a chronic disease with diverse pathologic manifestations and is accompanied by lipidmetabolism disorders and circulatory disorders as well as glycometabolism disorders. As the results, diabetes tends to progress entailing various complications in many cases. Therefore, it is necessary to select the drug of choice for the prevailing disease state in each individual case. However, this selection is often difficult in clinical settings because single use of each individual drug can not bring sufficient effects in some disease states and there are various problems such as side effect which is caused by an increased dose or a long-term administration.

SUMMARY OF THE INVENTION

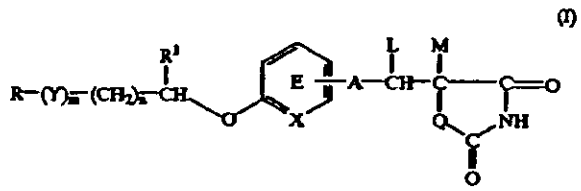
In view of the above state of the art, the inventors of the present invention did much research to develop antidiabetics which would not virtually cause adverse reactions even on long-term administration and could be effective for a large cohort of the diabetic population. As a consequence, they

discovered that the above object can be accomplished by using an insulin sensitivity enhancer, such as the drug described above, in combination with other antidiabetics differing from said enhancer in the mechanism of action, and accordingly have perfected the present invention.

The present invention, therefore, relates to:

1) Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with at least one member of the group consisting of an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor;

2) Pharmaceutical composition according to 1), wherein the insulin sensitivity enhancer is a compound represented by the formula:



(I)

wherein R represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR^3— (wherein R^3 represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R^1 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 substituents, and the substituents may optionally be combined with R^1 to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; or a pharmacologically acceptable salt thereof;

3) Pharmaceutical composition according to 2), wherein the compound represented by the formula (I) is pioglitazone;

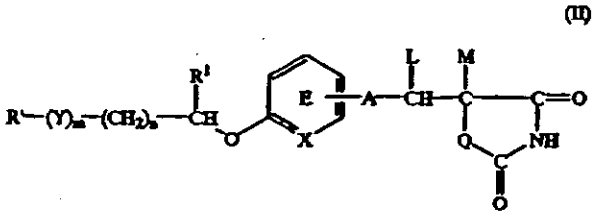
4) Pharmaceutical composition according to 1), which comprises an insulin sensitivity enhancer in combination with an α-glucosidase inhibitor;

5) Pharmaceutical composition according to 4), wherein the α-glucosidase inhibitor is voglibose;

6) Pharmaceutical composition according to 4), wherein the insulin sensitivity enhancer is pioglitazone and the α-glucosidase inhibitor is voglibose;

7) Pharmaceutical composition according to 1), which is for prophylaxis or treatment of diabetes;

8) Pharmaceutical composition which comprises a compound represented by the formula:

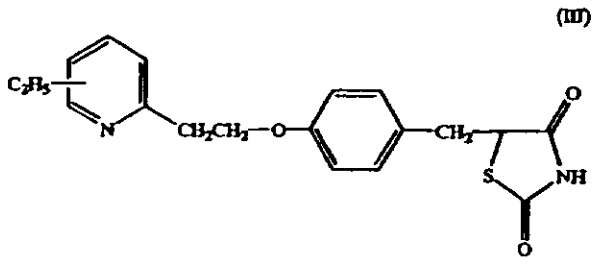


(II)

wherein R' represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR^3— (wherein R^3 represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents

a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R^1 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 substituents, and the substituents may optionally be combined with R^1 to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; with a proviso that R' does not represent benzopyranyl group when m and n are O, X represents CH, A represents a bond, Q represents sulfur atom, R^1, L and M represent hydrogen atom and ring E does not have further substituents; or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation;

9) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is the compound represented by the formula:



10) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is pioglitazone;

11) Pharmaceutical composition according to 8), wherein the insulin secretion enhancer is glibenclamide;

12) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is pioglitazone and the insulin secretion enhancer is glibenclamide;

13) Pharmaceutical composition according to 8), which is for prophylaxis or treatment of diabetes.

DETAILED DESCRIPTION OF THE INVENTION

The term "insulin sensitivity enhancer" as used in this specification means any and all drug substances that restore the impaired insulin receptor function to deblock insulin resistance and consequently enhance insulin sensitivity. As examples of the insulin sensitivity enhancer, the compound represented by the formula (I) or a pharmacologically acceptable salt thereof can be mentioned.

In the formula (I), as the hydrocarbon group in the optionally substituted hydrocarbon group represented by R, mention is made of aliphatic hydrocarbon groups, alicyclic hydrocarbon groups, alicyclic-aliphatic hydrocarbon groups, aromatic aliphatic hydrocarbon groups and aromatic hydrocarbon groups. Number of carbon atoms in these hydrocarbon groups is preferably 1 to 14.

The aliphatic hydrocarbon groups are preferably those having 1 to 8 carbon atoms. As the aliphatic hydrocarbon groups, mention is made of C_{1-8} saturated aliphatic hydrocarbon groups (e.g. alkyl group) as exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, hexyl, isohexyl, heptyl and octyl, and C_{2-8} unsaturated aliphatic hydrocarbon groups (e.g. alkenyl group, alkadienyl group, alkynyl group, alkadiynyl group) as exemplified by vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptynyl and 1-octynyl.

The alicyclic hydrocarbon groups are preferably those having 3 to 7 carbon atoms. As the alicyclic hydrocarbon groups, mention is made of C_{3-7} saturated alicyclic hydrocarbon groups (e.g. cycloalkyl group) as exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and C_{5-7} unsaturated alicyclic hydrocarbon groups (e.g. cycloalkenyl group, cycloalkadienyl group) as exemplified by 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl and 2,4-cycloheptadienyl.

As the alicyclic-aliphatic hydrocarbon groups, mention is made of, among those formed by combination of the above-mentioned alicyclic hydrocarbon groups with aliphatic hydrocarbon groups (e.g. cycloalkyl-alkyl group, cycloalkenyl-alkyl group), ones having 4 to 9 carbon atoms as exemplified by cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl and cycloheptylethyl.

The aromatic aliphatic hydrocarbon groups are preferably those having 7 to 13 carbon atoms (e.g. aralkyl group). As the aromatic aliphatic hydrocarbon groups, mention is made of C_{7-9} phenylalkyl as exemplified by benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and 1-phenylpropyl, and C_{11-13} naphthylalkyl as exemplified by α-naphthylmethyl, α-naphthylethyl, β-naphthylmethyl and β-naphthylethyl.

As the aromatic hydrocarbon groups, mention is made of, ones having 6 to 14 carbon atoms as exemplified by phenyl, naphthyl (α-naphtyl, β-naphthyl).

In the formula (I), as the heterocyclic group in the optionally substituted heterocyclic group represented by R, mention is made of, for example, 5- to 7-membered heterocyclic groups containing, as a ring component atom, 1 to 4 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom, and a condensed ring group. As the condensed ring, mention is made of, for example, these 5- to 7-membered heterocyclic groups condensed with 6-membered ring containing one or two nitrogen atoms, benzene ring or 5-membered ring containing one sulfur atom.

Examples of these heterocyclic groups include 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3 -pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl,, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, 1H-indazol-3-yl, 1H-pyrrolo [2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 1H-imidazo[4,5-b]pyrazin-2-yl and benzopyranyl. Among them, pyridyl, oxazolyl or thiazolyl group is preferable.

In the formula (I), the hydrocarbon group and heterocyclic group represented by R may optionally have 1 to 5, prefer-

ably 1 to 3 substituents at any substitutable positions. Examples of such substituents include aliphatic hydrocarbon group, alicyclic hydrocarbon group, aryl group, aromatic heterocyclic group, non-aromatic heterocyclic group, halogen atom, nitro group, optionally substituted amino group, optionally substituted acyl group, optionally substituted hydroxyl group, optionally substituted thiol group, optionally esterified carboxyl group, amidino group, carbamoyl group, sulfamoyl group, sulfo group, cyano group, azido group and nitroso group.

Examples of the aliphatic hydrocarbon groups include C_{1-15} straight-chain or branched aliphatic hydrocarbon groups as exemplified by alkyl group, alkenyl group, and alkynyl group.

Preferable examples of the alkyl group include C_{1-10} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, hexyl, pentyl, octyl, nonyl and decyl.

Preferable examples of the alkenyl group include C_{2-10} alkenyl groups such as vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl.

Preferable examples of the alkynyl group include C_{2-10} alkynyl groups such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As the alicyclic hydrocarbon group, mention is made of C_{3-12} saturated or unsaturated alicyclic hydrocarbon groups as exemplified by cycloalkyl group, cycloalkenyl group and cycloalkadienyl group.

Preferable examples of cycloalkyl group include C_{3-10} cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl and bicyclo[4.3.1]decyl.

Preferable examples of the cycloalkenyl group include C_{3-10} cycloalkenyl groups such as 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl and 3-cyclohexen-1-yl.

Preferable examples of the cycloalkadienyl group include C_{4-10} cycloalkadienyl groups such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl and 2,5-cyclohexadien-1-yl.

Preferable examples of the aryl group include C_{6-14} aryl groups such as phenyl, naphthyl (1-naphthyl, 2-naphthyl), anthryl, phenanthryl and acenaphthylenyl.

Preferable examples of the aromatic heterocyclic group include aromatic monocyclic heterocyclic groups such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 12,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl; and aromatic condensed heterocyclic groups such as benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, 1,2-benzoisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylidinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenathridinyl, phenathrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl.

Preferable examples of the non-aromatic heterocyclic group include oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidino, piperidino, morpholino and thiomorpholino.

Examples of the halogen atom include fluorine, chlorine, bromine and iodine.

As the substituted amino group in the optionally substituted amino group, mention is made of, N-monosubstituted amino group and N,N-disubstituted amino group. Examples of the substituted amino groups include amino groups having one or two substituents selected from C_{1-10} alkyl group, C_{2-10} alkenyl group, C_{2-10} alkynyl group, aromatic group, heterocyclic group and C_{1-10} acyl group (e.g. methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclohexylamino, phenylamino, N-methyl-N-phenyl-amino, acetylamino, propionylamino, benzoylamino and nicotinoylamino) As the acyl group, mention is made of C_{1-13} acyl groups such as C_{1-10} alkanoyl group, C_{3-10} alkenoyl group, C_{4-10} cycloalkanoyl group, C_{4-10} cycloalkenoyl group and C_{6-12} aromatic carbonyl group.

Preferable examples of the C_{1-10} alkanoyl group include formyl acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl and octanoyl. Preferable examples of the C_{3-10} alkenoyl group include acryloyl, methacryloyl, crotonoyl and isocrotonoyl. Preferable examples of C_{4-10} cycloalkanoyl group include cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl and cycloheptanecarbonyl. Preferable examples of C_{4-10} cycloalkenoyl group include 2-cyclohexenecarbonyl. Preferable examples of C_{6-12} aromatic carbonyl group include benzoyl, naphthoyl and nicotinoyl.

As the substituent in the substituted acyl group, mention is made of, for example, C_{1-3} alkyl group, C_{1-3} alkoxy group, halogen atom (e.g. chlorine, fluorine, bromine, etc.), nitro group, hydroxyl group and amino group.

As the substituted hydroxyl group in the optionally substituted hydroxyl group, mention is made of, for example, alkoxy group, cycloalkyloxy group, alkenyloxy group, cycloalkenyloxy group, aralkyloxy group, acyloxy group and aryloxy group.

Preferable examples of the alkoxy group include C_{1-10} alkoxy groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, t.-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy and nonyloxy. Preferable examples of the cycloalkyloxy group include C_{3-10} cycloalkyloxy groups such as cyclobutoxy, cyclopentyloxy and cyclohexyloxy. Preferable examples of the alkenyloxy group include C_{2-10} alkenyloxy groups such as allyloxy, crotyloxy, 2-pentenyloxy and 3-hexenyloxy. Preferable examples of the cycloalkenyloxy group include C_{3-10} cycloalkenyloxy groups such as 2-cyclopentenyloxy and 2-cyclohexenyloxy. Preferable examples of the aralkyloxy group include C_{7-10} aryloxy groups such as phenyl-C_{1-4}alkyloxy (e.g. benzyloxy and phenethyloxy). Preferable examples of the acyloxy group include C_{2-13} acyloxy group, more preferably C_{2-4} alkanoy-

loxy groups (e.g. acetyloxy, propionyloxy, butyryloxy and isobutyryloxy). Preferable examples of the aryloxy group include C_{6-14} aryloxy groups such as phenoxy and naphthyloxy. The aryloxy group may optionally have one or two substituents such as halogen atom (e.g. chlorine, fluorine, bromine). Examples of the substituted aryloxy group include 4-chlorophenoxy.

As the substituted thiol group in the optionally substituted thiol group, mention is made of, alkylthio group, cycloalkylthio group, alkenylthio group, cycloalkenylthio group, aralkylthio group, acylthio group and arylthio group.

Preferable examples of the alkylthio group include C_{1-10} alkylthio groups such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec.-butylthio, t.-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio and nonylthio. Preferable examples of the cycloalkylthio group include C_{3-10} cycloalkylthio groups such as cyclobutylthio, cyclopentylthio and cyclohexylthio. Preferable examples of the alkenylthio group include C_{2-10} alkenylthio groups such as allylthio, crotylthio, 2-pentenylthio and 3-hexenylthio. Preferable examples of the cycloalkenylthio group include C_{3-10} cycloalkenylthio groups such as 2-cyclopentenylthio and 2-cyclohexenylthio. Preferable examples of the aralkylthio include C_{7-10} aralkylthio groups such as phenyl-C_{1-4}alkylthio (e.g. benzylthio and phenethylthio). Preferable examples of the acylthio group include C_{2-13} acylthio group, more preferably C_{2-4} alkanoylthio groups (e.g. acetylthio, propionylthio, butyrylthio and isobutyrylthio).

Preferable examples of the arylthio group include C_{6-14} arylthio groups such as phenylthio and naphthylthio. The arylthio group may optionally have one or two substituents such as halogen atom (e.g. chlorine, fluorine, bromine). Examples of the substituted arylthio group include 4-chlorophenylthio.

As the optionally esterified carboxyl group, mention is made of, for example, alkoxycarbonyl group, aralkyloxycarbonyl group and aryloxycarbonyl group.

Preferable examples of the alkoxycarbonyl group include C_{2-5} alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and butoxycarbonyl. Preferable examples of the aralkyloxycarbonyl group include C_{8-10} aralkyloxycarbonyl groups such as benzyloxycarbonyl. Preferable examples of the aryloxycarbonyl group include C_{7-15} aryloxycarbonyl groups such as phenoxycarbonyl and p-tolyloxycarbonyl.

Among the substituents on the hydrocarbon group and heterocyclic group represented by R, C_{1-10} alkyl groups, aromatic heterocyclic groups and C_{6-14} aryl groups are preferable, and C_{1-3} alkyl, furyl, thienyl, phenyl and naphthyl are especially preferable.

In the formula (I), substituents on the hydrocarbon group and heterocyclic group which are represented by R, may, when they are alicyclic hydrocarbon group, aryl group, aromatic heterocyclic group or non-aromatic heterocyclic group, have one or more, preferably 1 to 3, of suitable substituents respectively. Examples of these substituents include C_{1-6} alkyl groups, C_{2-6} alkenyl groups, C_{2-6} alkynyl groups, C_{3-7} cycloalkyl groups, C_{6-14} aryl groups, aromatic heterocyclic groups (e.g. thienyl, furyl, pyridyl, oxazolyl and thiazolyl), non-aromatic heterocyclic groups (e.g. tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolidino and piperazino), C_{7-9} aralkyl groups, amino group, N-mono-C_{1-4} alkylamino groups, N,N-di-C_{1-4} alkylamino groups, C_{2-8} acylamino groups (e.g. acetylamino, propionylamino and benzoylamino), amidino group, C_{2-8} acyl group (e.g. C_{2-8} alkanoyl groups), carbamoyl group, N-mono-C_{1-4} alkyl carbamoyl groups, N,N-di-C_{1-4} alkyl carbamoyl groups, sulfamoyl group, N-mono-C_{1-4} alkyl sulfamoyl groups, N,N-di-C_{1-4} alkyl sulfamoyl groups, carboxyl group, C_{2-8} alkoxycarbonyl groups, hydroxyl group, C_{1-4} alkoxy groups, C_{2-5} alkenyloxy groups, C_{3-7} cycloalkyloxy groups, C_{7-9} aralkyloxy groups, C_{6-14} aryloxy groups, mercapto group, C_{1-4} alkylthio groups, C_{7-9} aralkylthio groups C_{6-14} arylthio groups, sulfo group, cyano group, azido group, nitro group, nitroso group and halogen atom.

In the formula (I), R is preferably an optionally substituted heterocyclic group. R is more preferably pyridyl, oxazolyl or thiazolyl group which is optionally substituted by 1 to 3 substituents selected from C_{1-3} alkyl group, furyl group, thienyl group, phenyl group and naphthyl group.

R' in the formula (II) has the same definition as R except that R' does not represent benzopyranyl group when m and n are 0; X represents CH; A represents a bond; Q represents sulfur atom; R^1, L and M represent hydrogen atom; and ring E does not have further substituents.

In the formulae (I) and (II), Y represents —CO—, —CH(OH)— or —NR^3— (wherein R^3 represents an optionally substituted alkyl group), preferably —CH(OH)— or —NR^3—. As the alkyl group in the optionally substituted alkyl group represented by R^3, mention is made of, for example, C_{1-4} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl and t.-butyl. Examples of the substituents include halogen (e.g., fluorine, chlorine, bromine and iodine), C_{1-4} alkoxy groups (e.g. methoxy, ethoxy, propoxy, butoxy, isobutoxy, sec.-butoxy and t.-butoxy), hydroxyl group, nitro group and C_{1-4} acyl groups (e.g. formyl, acetyl and propionyl).

The symbol m is 0 or 1, preferably 0.

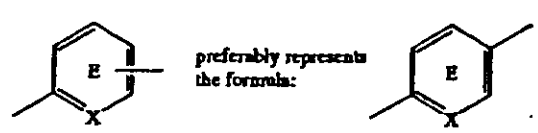
The symbol n is 0, 1 or 2, preferably 0 or 1.

X represents CH or N, preferably CH.

In the formulae (I) and (II), A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group. The aliphatic hydrocarbon group may be straight-chain or branched, and saturated or unsaturated. Specific examples of the aliphatic hydrocarbon group include saturated ones [e.g. —CH_2—, —$CH(CH_3)$—, —$(CH_2)_2$—, —$CH(C_2H_5)$—, —$(CH_2)_3$—, —$(CH_2)_4$—, —$(CH_2)_5$—, —$(CH_2)_6$— and —$(CH_2)_7$—] and unsaturated ones [e.g. —CH=CH—, —$C(CH_3)$=CH—, —CH=CH—CH_2—, —$C(C_2H_5)$—CH—, —CH_2—CH=CH—CH_2—, —CH_2—CH_2—CH=CH—CH_2—. —CH=CH—CH=CH—CH_2— and —CH=CH—CH=CH—CH=CH—CH_2—. A is preferably a bond or C_{1-4} divalent aliphatic hydrocarbon groups, the aliphatic hydrocarbon groups preferably being saturated. A is more preferably a bond or —$(CH_2)_2$—.

As the alkyl group represented by R^1, substantially the same one as the alkyl group in the above-mentioned R^3. R^1 is preferably hydrogen atom.

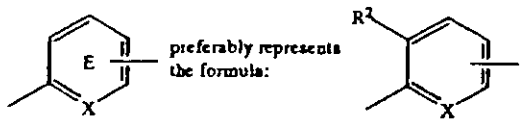
In the formulae (I) and (II), the partial formula:



Ring E has 1 to 4 substituents at any substitutable positions. Examples of such substituents include alkyl group, optionally substituted hydroxyl group, halogen atom, optionally substituted acyl group and optionally substituted amino group. These substituents have substantially the same

meaning as those described as substituents of the hydrocarbon group and heterocyclic group represented by R.

Ring E, namely the partial formula:



wherein R^2 represents hydrogen atom, an alkyl group, an optionally substituted hydroxyl group, a halogen atom, an optionally substituted acyl group, nitro group or an optionally substituted amino group.

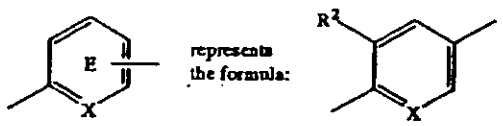
As the alkyl group, optionally substituted hydroxyl group, halogen atom, optionally substituted acyl group and optionally substituted amino group represented by R^2, mention is made of those described as substituents of the hydrocarbon group and heterocyclic group represented by R. R^2 is preferably hydrogen atom, optionally substituted hydroxyl group or halogen atom, more preferably hydrogen atom or optionally substituted hydroxyl group, especially preferably hydrogen atom or C_{1-4} alkoxy groups.

In the formulae (I) and (II), L and M represent hydrogen atom, or they may optionally be combined with each other to form a bond. L and M are preferably hydrogen atom.

In the compounds wherein L and M are combined with each other to form a bond, there exist (E) and (Z)-isomers relative to the double bond at the 5-position of the azolidinedione ring.

And, in the compounds wherein L and M respectively represent hydrogen atom, there exist (R)- and (S)-optical isomers due to the asymmetric carbon at the 5-position of the azolidinedione ring. The compounds include these (R)- and (S)-optical isomers and racemic isomers.

Preferable examples of the compounds represented by the formula (I) or (II) includes those in-which R is pyridyl, oxazolyl or thiazolyl group optionally having 1 to 3 substituents selected from C_{1-3} alkyl, furyl, thienyl, phenyl and naphthyl; m is 0; n is 0 or 1; X is CH; A is a bond or $-(CH_2)_2-$; R^1 is hydrogen atom; ring E, namely the partial formula:



and R^2 is hydrogen atom or C_{1-4} alkoxy group; and L and M are both hydrogen atom.

Preferable examples of the compound represented by the formula (I) include

(1) the compound represented by the formula (III) such as 5-[4-[2-(3-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione; 5-[4-[2-(4-ethyl-2-pyridyl)ethoxy]-benzyl]-2,4-thiazolidinedione; 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (generic name: pioglitazone); and 5-[4-[2-(6-ethyl-2-pyridyl) ethoxy]benzyl]-2,4-thiazolidinedione;

(2) (R)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione; and

(3) 5-[[4-f(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (generic name: troglitazone/CS-045).

The compound represented by the formula (I) is especially preferably pioglitazone.

The compound represented by the formula (II) is preferably the compound represented by the formula (III) and (R)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione, more preferably pioglitazone.

The pharmacologically acceptable salt of the compound represented by the formula (I) or (II) are exemplified by salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

Preferable examples of salts with inorganic bases include salts with alkali metals such as sodium, potassium, etc., salts with alkaline earth metals such as calcium, magnesium, etc., and salts with aluminum, ammonium, etc.

Preferable examples of salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, etc.

Preferable examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.

Preferable examples of salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid., benzenesulfonic acid, p-toluenesulfonic acid, etc.

Preferable examples of salts with basic amino acids include salts with arginine, lysine, ornithine, etc., and preferable examples of salts with acidic amino acids include salts with aspartic acid, glutamic acid, etc.

The pharmacologically acceptable salt of the compound represented by the formula (III) is preferably a salt with an inorganic acid, more preferably a salt with hydrochloric acid. Especially, pioglitazone is preferably used in the form of salt with hydrochloric acid.

The compounds represented by the formula (I) or (II) or a salt thereof can be produced in accordance with, for example, methods described in JPA S55(1980)-22636(EP-A 8203), JPA S60(1985)-208980(EP-A 155845), JPA S61 (1986)-286376(EP-A 208420), JPA S61(1986)-85372(EP-A 177353), JPA S61(1986)-267580(EP-A 193256), JPA H5(1993)-86057(WO 92/18501), JPA H7(1995)-82269 (EP-A 605228), JPA H7(1995)-101945(EP-A 612743), EP-A 643050, EP-A 710659, etc. or methods analogous thereto.

Insulin sensitivity enhancers include 5-[[3,4-dihydro-2-(phenylmethyl)-2H-1-benzopyran-6-yl]methyl]-2,4-thiazolidinedione (generic name: englitazone) or its sodium salt;

5-[[4-[3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl] phenyl]methyl]-2,4-thiazolidinedione (generic name: darglitazone/CP-86325) or its sodium salt;

5-[2-(5-methyl-2-phenyl-4-oxazolylmethyl)benzofuran-5-ylmethyl]-2,4-oxazolidinedione (CP-92768);

5-(2-naphthalenylsulfonyl)-2,4-thiazolidinedione (AY-31637);

4-[(2-naphthalenyl)methyl]-3H-1,2,3,5-oxathiadiazol-2-oxide (AY-30711); and

5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]-methyl]-2,4-thiazolidinedione (BRL-49653), etc. in addition to compounds mentioned hereinbefore.

In the present invention, examples of the drug which is used in combination with the above-mentioned insulin sensitivity enhancer include an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor.

α-Glucosidase inhibitors are drugs which inhibit digestive enzymes such as amylase, maltase, α-dextrinase, sucrase, etc. to-retard digestion of starch and sugars. Examples of the α-glucosidase inhibitors include acarbose, N-(1,3-dihydroxy-2-propyl)valiolamine (generic name; voglibose), miglitol, etc. with preferance given to voglibose.

Aldose reductase inhibitors are drugs which inhibit the first-stage rate-limitting enzyme in the polyol pathway to prevent or arrest diabetic complications. In the hyperglycemic state of diabetes, the utilization of glucose in the polyol pathway is increased and the excess sorbitol accumulated intracellularly as a consequence acts as a tissue toxin and hence evokes the onset of complications such as diabetic neuropathy, retinopathy, and nephropathy. Examples of the aldose reductase inhibitors include tolurestat; epalrestat; 3,4-dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxazine-4-acetic acid; 2,7-difluorospiro(9H-fluorene-9,4'-imidazolidine)-2',5'-dione (generic name: imirestat);

3-[(4-bromo-2-fluorophenyl)methyl]-7-chloro-3,4-dihydro-2,4-dioxo-1(2H)-quinazoline acetic acid (generic name: zenarestat);

6-fluoro-2,3-dihydro-2',5'-dioxo-spiro[4H-1-benzopyran-4,4'-imidazolidine]-2-carboxamide (SNK-860);

zopolrestat; sorbinil; and

1-[(3-bromo-2-benzofuranyl)sulfonyl]-2,4-imidazolidinedione (M-16209), etc.

Biguanides are drugs having actions of stimulation of anaerobic glycolysis, increase of the sensitivity td insulin in the peripheral tissues, inhibition of glucose absorption from the intestine, suppression of hepatic gluconeogenesis, and inhibition of fatty acid oxidation. Examples of the biguanides include phenformin, metformin, buformin etc.

Statin compounds are drugs having actions of lowering blood cholesterol levels by inhibiting hydroxymethylglutalyl CoA (HMG-CoA) reductase. Examples of the statin compounds include pravastatin and its sodium salt, simvastatin, lovastatin, atorvastatin, fluvastatin, etc.

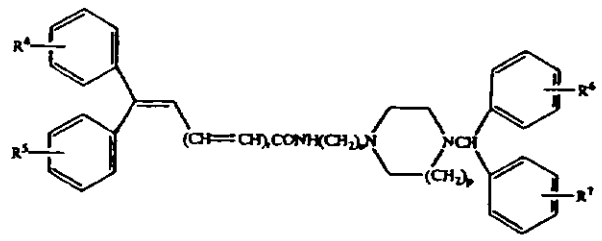
Squalene synthesis inhibitors are drugs having actions of lowering blood cholesterol levels by inhibiting synthesis of squalene. Examples of the squalene synthesis inhibitors include (S)-α-[Bis[2,2-dimethyl-1-oxopropoxy)methoxy] phosphinyl]-3-phenoxybenzenebutanesulfonic acid, mono potassium salt (BMS-188494).

Fibrate compounds are drugs having actions of lowering blood cholesterol levels by inhibiting synthesis and secretion of triglycerides in liver and activating a lipoprotein lipase.

Examples of the fibrate compounds include bezafibrate, beclobrate, binifibrate, ciplofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate, etc.

LDL catabolism enhancers are drugs having actions of lowering blood cholesterol levels by increasing the number of LDL (low-density lipoprotein) receptors.

Examples of the LDL catabolism enhancers include the compound which is described in JPA H7(1995)-316144 and represented by the formula:



wherein R^4, R^5, R^6 and R^7 are the same or different, and represent hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group; r is 0–2; s is 2–4; p is 1–2; or a salt thereof; specifically N-[2-[4-bis(4-fluorophenyl) methyl-1-piperazinyl]ethyl]-7,7-diphenyl-2,4,6-heptatrienic acid amide, etc.

The above-mentioned statin compounds, squalene synthesis inhibitors, fibrate compounds and LDL catabolism enhancers can be substituted with other drugs having the property to lower blood cholesterol and triglyceride levels. Examples of these drugs include nicotinic acid derivatives such as nicomol and niceritrol; antioxidants such as probucol; and ion-exchange resins such as colestyramin.

Angiotensin converting enzyme inhibitors are drugs having actions of partially lowering blood glucose levels as well as lowering blood pressure by inhibiting angiotensin converting enzymes. Examples of the angiotensin converting enzyme inhibitors include captopril, enalapril, alacepril, delapril, ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moveltopril, perindopril, quinapril, spirapril, temocapril, trandolapril, etc.

In the present invention, especially preferred is, the pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with an α-glucosidase inhibitor. The insulin sensitivity enhancer is especially preferably pioglitazone, and the β-glucosidase inhibitor is especially preferably voglibose.

In the present invention, examples of the drug which is used in combination with the compound represented by the formula (II) or a pharmacologically acceptable salt thereof include an insulin secretion enhancer and/or an insulin preparation.

Insulin secretion enhancers are drugs having the property to promote secretion of insulin from pancreatic β cells. Examples of the insulin secretion enhancers include sulfonylureas (SU). The sulfonylureas (SU) are drugs which promote secretion of insulin from pancreatic β cells by transmitting signals of insulin secretion via SU receptors in the cell membranes. Examples of the SU include tolbutamide; chlorpropamide; tolazamide; acetohexamide; 4-chloro-N-[(1-pyrolidinylamino)carbonyl]-benzenesulfonamide (generic name: glycopyramide) or its ammonium salt; glibenclamide (glyburide); gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; tolcyclamide, etc.

Insulin secretion enhancers include N-[[4-(1-methylethyl) cyclohexyl]carbonyl]-D-phenylalanine (AY-4166); calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl) propionate dihydrate (KAD-1229); and glimepiride (Hoe 490), etc. in addition to compounds mentioned hereinbefore. The insulin secretion enhancer is especially preferably glibenclamide.

Examples of the insulin preparations include animal insulin preparations typically extracted from bovine or porcine

pancreas and human insulin preparations synthesized by genetic engineering techniques typically using *Escherichia coli* or yeasts. While insulin preparations are available in a variety of types, e.g. immediate-acting, bimodal-acting, intermediate-acting, and long-acting, these types of preparations can be selectively administered according to the patient's condition.

In the present invention, especially preferred is the pharmaceutical composition which comprises the compound represented by the formula (II) or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer. The compound represented by the formula (II) or a pharmacologically acceptable salt thereof is especially preferably pioglitazone, and the insulin secretion enhancer is especially preferably glibenclamide.

The pharmaceutical composition comprising an insulin sensitivity enhancer in combination with at least one member selected from the group consisting of an a-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor; and the pharmaceutical composition comprising the compound represented by the formula (II) or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation, both provided in accordance with the present invention, can be respectively put to use by mixing the respective active components either all together or independently with a physiologically acceptable carrier, excipient, binder, diluent, etc. and administering the mixture or mixtures either orally or non-orally as a pharmaceutical composition. When the active components are formulated independently, the respective formulations can be extemporaneously admixed using a diluent or the like and administered or can be administered independently of each other, either concurrently or at staggered times to the same subject.

The dosage form for said pharmaceutical composition includes such oral dosage forms as granules, powders, tablets, capsules, syrups, emulsions, suspensions, etc. and such non-oral dosage forms as injections (e.g. subcutaneous, intravenous, intramuscular and intraperitoneal injections), drip infusions, external application forms (e.g. nasal spray preparations, transdermal preparations, ointments, etc.), and suppositories (e.g. rectal and vaginal suppositories).

These dosage forms can be manufactured by the per se known technique conventionally used in pharmaceutical procedures. The specific manufacturing procedures are as follows.

To manufacture an oral dosage form, an excipient (e.g. lactose, sucrose, starch, mannitol, etc.), a disintegrator (e.g. calcium carbonate, carboxymethylcellulose calcium, etc.), a binder (e.g. α-starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, etc.), and a lubricant (e.g. talc, magnesium stearate, polyethylene glycol 6000, etc.), for instance, are added to the active component or components and the resulting composition is compressed. Where necessary, the compressed product is coated, by the per se known technique, for masking the taste or for enteric dissolution or sustained release. The coating material that can be used includes, for instance, ethylcellulose, hydroxymethylcellulose, polyoxyethylene glycol, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, and Eudragit (Rohm & Haas, Germany, methacrylic-acrylic copolymer).

Injections can be manufactured typically by the following procedure. The active component or components are dissolved, suspended or emulsified in an aqueous vehicle (e.g. distilled water, physiological saline, Ringer's solution, etc.) or an oily vehicle (e.g. vegetable oil such as olive oil, sesame oil, cottonseed oil, corn oil, etc. or propylene glycol) together with a dispersant (e.g. Tween 80 (Atlas Powder, U.S.A.), HCO 60 (Nikko Chemicals), polyethylene glycol, carboxymethylcellulose, sodium alginate, etc.), a preservative (e.g. methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, benzyl alcohol, chlorobutanol, phenol, etc.), an isotonizing agent (e.g. sodium chloride, glycerol, sorbitol, glucose, inverted sugar, etc.) and other additives. If desired, a solubilizer (e.g. sodium salicylate, sodium acetate, etc.), a stabilizer (e.g. human serum albumin), a soothing agent (e.g. benzalkonium chloride, procaine hydrochloride, etc.) and other additives can also be added.

A dosage form for external application can be manufactured by processing the active component or components into a solid, semi-solid or liquid composition. To manufacture a solid composition, for instance, the active component or components, either as they are or in admixture with an excipient (e.g. lactose, mannitol, starch, microcrystalline cellulose, sucrose, etc.), a thickener (e.g. natural gums, cellulose derivatives, acrylic polymers, etc.), etc., are processed into powders. The liquid composition can be manufactured in substantially the same manner as the injections mentioned above. The semi-solid composition is preferably provided in a hydrous or oily gel form or an ointment form. These compositions may optionally contain a pH control agent (e.g. carbonic acid, phosphoric acid, citric acid, hydrochloric acid, sodium hydroxide, etc.), and a preservative (e.g. p-hydroxybenzoic acid esters, chlorobutanol, benzalkonium chloride, etc.), among other additives.

Suppositories can be manufactured by processing the active component or components into an oily or aqueous composition, whether solid, semi-solid or liquid. The oleaginous base that can be used includes, for instance, higher fatty acid glycerides [e.g. cacao butter, Witepsols (Dinamit-Nobel), etc.], medium-chain fatty acids [e.g. Migriols (Dinamit-Nobel), etc.], vegetable oils (e.g. sesame oil, soybean oil, cotton-seed oil, etc.), etc. The water-soluble base includes, for instance, polyethylene glycols, propylene glycol, etc. The hydrophilic base includes, for instance, natural gums, cellulose derivatives, vinyl polymers, and acrylic polymers, etc.

The pharmaceutical composition of the present invention is low in toxicity and can be safely used in mammals (e.g. humans, mice, rats, rabbits, dogs, cats, bovines, horses, swines, monkeys).

The dosage of the pharmaceutical composition of the present invention may be appropriately determined with reference to the dosages recommended for the respective active components and can be selected appropriately according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of the active components, among other factors. For example, the dosage of the insulin sensitivity enhancer for an adult can be selected from the clinical oral dose range of 0.01 to 10 mg/kg body weight (preferably 0.05 to 10 mg/kg body weight, more preferably 0.05 to 5 mg/kg body weight) or the clinical parenteral dose range of 0.005 to 10 mg/kg body weight (preferably 0.01 to 10 mg/kg body weight, more preferably 0.01 to 1 mg/kg body weight). The other active component or components having different modes of action for use in combination can also be used in dose ranges selected by referring to the respective recommended clinical dose ranges. The preferred frequency of administration is 1 to 3 times a day.

The proportions of the active components in the pharmaceutical composition of the present invention can be appropriately selected according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of active components, among other factors. When, for example, the compound represented by the formula (I) or a pharmacologically acceptable salt thereof (e.g. pioglitazone) which is the insulin sensitivity enhancer and voglibose which is an α-glucosidase inhibitor are to be administered in combination to a human subject, voglibose is used in a proportion of usually about 0.0001 to 0.2 weight parts and preferably about 0.001 to 0.02 weight parts relative to 1 weight part of the compound or a salt thereof. When, for example, the compound represented by the formula (II) or a pharmacologically acceptable salt thereof and glibenclamide which is an insulin secretion enhancer are to be administered in combination to a human subject, glibenclamide is used in a proportion of usually about 0.002 to 5 weight parts and preferably about 0.025 to 0.5 weight parts, relative to 1 weight part of the compound or a pharmacologically acceptable salt thereof.

The pharmaceutical composition of the present invention shows a marked synergistic effect compared with administration of either active component alone. For example, compared with cases in which each of these active components was administered to diabetic Wistar fatty rats with genetical obsesity, administration of these active components in combination resulted in marked improvements in both hyperglycemia and reduced glucose tolerance. Thus, the pharmaceutical composition of the present invention lowers blood glucose in diabetics more effectively than it is the case with administration of each component drug alone and, therefore, can be used advantageously for the prophylaxis and treatment of diabetic complications.

Furthermore, since the pharmaceutical composition of the present invention develops sufficient efficacy with reduced doses as compared with the administration of any one of the active components alone, the side effects of the respective components (e.g. gastrointestinal disorders such as diarrhea, etc.) can be reduced.

The following working examples and experimental examples are merely intended to illustrate the present invention in further detail but should by no means be construed as defining the scope of the invention.

The pharmaceutical composition of the present invention can be prepared according to the following formulations.

WORKING EXAMPLE 1

Capsules	
(1) Pioglitazone hydrochloride	30 mg
(2) Voglibose	0.2 mg
(3) Lactose	60 mg
(4) Microcrystalline cellulose	79.8 mg
(5) Magnesium stearate	10 mg
Total	180 mg

The whole amounts of (1), (2), (3) and (4) and half the amount of (5) are mixed well and granulated in the conventional manner. Then, the balance of (5) is added and, after mixing, the whole composition is filled in a gelatin hard capsule shell.

WORKING EXAMPLE 2

Tablets	
(1) Pioglitazone hydrochloride	10 mg
(2) Glibenclamide	1.25 mg
(3) Lactose	86.25 mg
(4) Corn starch	20 mg
(5) Polyethylene glycol	2.5 mg
(6) Hydroxypropylcellulose	4 mg
(7) Carmellose calcium	5.5 mg
(8) Magnesium stearate	0.5 mg
	130 mg (per tablet)

The whole amounts of (1), (2), (3), (4), and (5), ⅔ amounts of (6) and (7), and ½ amount of (8) are mixed well and granulated in the conventional manner. Then, the balances of (6), (7) and (8) are added to the granules, which is mixed well and the whole composition is compressed with a tablet machine. The adult dosage is 3 tablets/day, to be taken in 1 to 3 divided doses.

WORKING EXAMPLE 3

Capsules	
(1) Pioglitazone hydrochloride	18 mg
(2) Epalrestat	50 mg
(3) Lactose	55 mg
(4) Microcrystalline cellulose	55 mg
(5) Magnesium stearate	10 mg
Total	180 mg

The whole amounts of (1), (2), (3) and (4) and ½ amount of (5) are mixed well and granulated in the conventional manner. Then, the balance of (5) is added and the whole composition is filled in gelatin capsule shell. The adult dosage is 3 capsules/day, to be taken in 1 to 3 divided doses.

EXPERIMENTAL EXAMPLE 1

Effect of pioglitazone hydrochloride in combination with α-glucosidase inhibitor in genetically obese and diabetic Wistar fatty rats

Male Wistar fatty rats aged 14–19 weeks were divided into 4 groups of 5–6, and pioglitazone hydrochloride (1 mg/kg body wt./day, p.o.) and/or voglibose (an α-glucosidase inhibitor) (0.31 mg/kg body wt./day; administered by mixing in commercial diet at a rate of 5 ppm) was administered for 14 days. The blood was then collected from the tail vein and the plasma glucose and hemoglobin A_1 were determined by the enzymatic method (Encore Chemical System, Baker) and using a commercial kit (NC-ROPET, Nippon Chemiphar Co.), respectively. The results were expressed in mean±standard deviation for each group (n=5–6) and analyzed by Dunnett's test, which are shown in Table 1. The 1% level of significance was used.

TABLE 1

Group	Plasma glucose (mg/dl)	Hemoglobin A_1 (%)
Control	345 ± 29	5.7 ± 0.4
Pioglitazone	215 ± 50*	5.2 ± 0.3

TABLE 1-continued

Group	Plasma glucose (mg/dl)	Hemoglobin A_1 (%)
Voglibose	326 ± 46	6.0 ± 0.6
Pioglitazone + voglibose	114 ± 23*	4.5 ± 0.4*

*:P < 0.01 vs. control group

It is apparent from Table 1 that both the blood glucose and hemoglobin A_1 levels were remarkably lowered by combined administration of pioglitazone and voglibose as compared with the administration of either drug alone.

EXPERIMENTAL EXAMPLE 2

Effect of pioglitazone hydrochloride in combination with an insulin secretion enhancer in genetically obese and diabetic Wistar fatty rats

Male Wistar fatty rats aged 13–14 weeks were divided into 4 groups of 5, and pioglitazone hydrochloride (3 mg/kg/day, p.o.) and/or glibenclamide (an insulin secretion enhancer) (3 mg/kg/day, p.o) was administered for 7 days. Following an overnight fast, the oral glucose loading test (2 g glucose/kg/5 ml, p.o.) was carried out. Prior to glucose loading and 120 and 240 minutes after the loading, blood was collected from the tail vein and the plasma glucose was assayed by the enzymatic method (Encore Chemical System, Baker). The results were expressed in mean±SD for each group (n=5) and analyzed by Dunnett's test, which are shown in Table 2.

TABLE 2

Group	Plasma glucose (mg/dl) 0 min.	120 min.	240 min.
Control	119 ± 9	241 ± 58	137 ± 10
Pioglitazone	102 ± 12	136 ± 17*	102 ± 9*
Glibenclamide	118 ± 12	222 ± 61	106 ± 24*
Pioglitazone + glibenclamide	108 ± 3	86 ± 10*	60 ± 5*

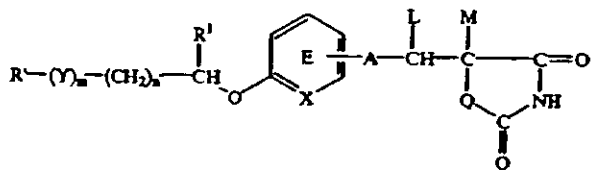
*: P<0.01 vs. control group

The pharmaceutical composition of the present invention shows a potent depressive effect on diabetic hyperglycemia and is useful for prophylaxis and treatment of diabetes. Moreover, this pharmaceutical composition is useful for prophylaxis and treatment of diabetic complications such as diabetic neuropathy, nephropathy, retinopathy, macroangiopathy, and osteopenia. In addition, by appropriately selecting the kinds of component drugs, administration route dosage, etc. according to clinical status, stable hypoglycemic efficacy in long-term therapy can be expected with an extremely low risk of side effect.

What is claimed is:

1. A method for treating lipid metabolism disorders in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound represented by the formula:

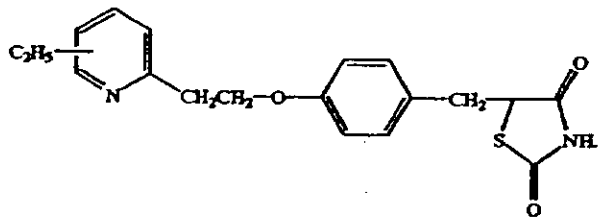
(II)



wherein R' represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR^3— wherein R^3 represents an optionally substituted alkyl group; m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R^1 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 further substituents, and the substituents may optionally be combined with R^1 to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; with a proviso that R' does not represent benzopyranyl group when m and n are O, X represents CH, A represents a bond, Q represents sulfur atom, R^1, L and M represent hydrogen atoms and ring E does not have further substituents; or a pharmacologically acceptable salt thereof, in combination with an insulin secretion enhancer.

2. The method according to claim 1, wherein the compound represented by the formula (II) is the compound represented by the formula:

(III)



3. The method according to claim 1, wherein the compound represented by the formula (II) is pioglitazone.

4. The method according to claim 1, wherein the insulin secretion enhancer is glibenclamide.

5. The method according to claim 1, wherein the compound represented by the formula (II) is pioglitazone and the insulin secretion enhancer is glibenclamide.

6. The method according to claim 1, wherein the compound is 5-[[4-2-(methyl-2-pyridylamino) ethoxy]phenyl]-methyl]-2,4, -thiazolidinedione or its pharmacologically acceptable salt thereof.

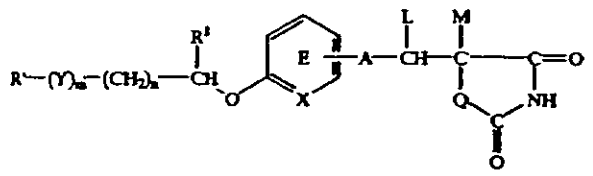
7. The method according to claim 1, wherein the compound represented by the formula (II) is troglitazone.

8. The method according to claim 1, wherein the insulin secretion enhancer is a sulfonylurea.

9. The method according to claim 8, wherein the sulfonylurea is selected from tolbutamide, chlorpropamide, tolazamide, acetohexamide, 4-chloro-N-[(1-pyrolidinylamino)carbonyl]-benzenesulfonamide or its ammonium salt, glibenclamide, gliclazide, 1-butyl-3-metanilylurea, carbutamide, glibonuride, glipizide, gliquidone, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide and tolcyclamide.

10. A method for treating glycometabolism disorders in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound represented by the formula:

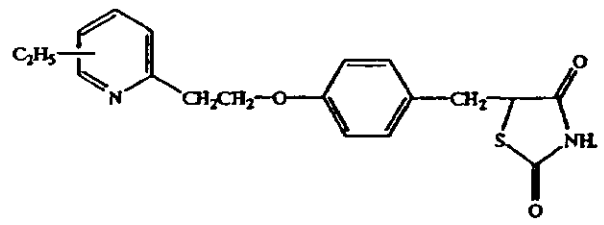
(II)



wherein R' represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR^3— wherein R^3 represents an optionally substituted alkyl group; m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R^1 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 further substituents, and the substituents may optionally be combined with R^1 to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; with a proviso that R' does not represent benzopyranyl group when m and n are O, X represents CH, A represents a bond, Q represents sulfur atom, R^1, L and M represent hydrogen atoms and ring E does not have further substituents; or a pharmacologically acceptable salt thereof, in combination with an insulin secretion enhancer.

11. The method according to claim 10, wherein the compound represented by the formula (II) is the compound represented by the formula:

(III)



12. The method according to claim 10, wherein the compound represented by the formula (II) is pioglitazone.

13. The method according to claim 10, wherein the insulin secretion enhancer is glibenclamide.

14. The method according to claim 10, wherein the compound represented by the formula (II) is pioglitazone and the insulin secretion enhancer is glibenclamide.

15. The method according to claim 10, wherein the compound is 5-[[4-2-(methyl-2-pyridylamino) ethoxy] phenyl]-methyl]-2,4, -thiazolidinedione or its pharmacologically acceptable salt thereof.

16. The method according to claim 10, wherein the compound represented by the formula (II) is troglitazone.

17. The method according to claim 10, wherein the insulin secretion enhancer is a sulfonylurea.

18. The method according to claim 17, wherein the sulfonylurea is selected from tolbutamide, chlorpropamide, tolazamide, acetohexamide, 4-chloro-N-[(1-pyrolidinylamino)carbonyl]-benzenesulfonamide or its ammonium salt, glibenclamide, gliclazide, 1-butyl-3-metanilylurea, carbutamide, glibonuride, glipizide, gliquidone, glisoxepid, glybuthiazole, glibuzole, glybexamide, glymidine, glypinamide, phenbutamide and tolcyclamide.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,150,383
DATED : November 21, 2000
INVENTOR(S) : Ikeda et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 18,
Line 23, change "m and n are O" to -- m and n are 0 --;
Line 52, change "4-2-" to -- 4-[2- --;
Line 53, change "2,4,-" to -- 2,4- --.

Column 19,
Line 29, change "m and n are O" to -- m and n are 0 --.

Column 20,
Line 21, change "4-2-" to -- 4-[2- --;
Line 22, change "2,4-" to -- 2,4- --.

Signed and Sealed this

Twenty-sixth Day of February, 2002

Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

D

US006166042A

United States Patent [19]

Ikeda et al.

[11] **Patent Number: 6,166,042**

[45] **Date of Patent: Dec. 26, 2000**

[54] **PHARMACEUTICAL COMPOSITION**

[75] Inventors: Hitoshi Ikeda, Higashiosaka; Takashi Sohda, Takatsuki; Hiroyuki Odaka, Kobe, all of Japan

[73] Assignee: Takeda Chemical Industries, Ltd., Osaka, Japan

[21] Appl. No.: 09/302,470

[22] Filed: Apr. 30, 1999

Related U.S. Application Data

[62] Division of application No. 09/057,465, Apr. 9, 1998, Pat. No. 5,965,584, which is a division of application No. 08/667,979, Jun. 19, 1996, Pat. No. 5,952,356.

[30] **Foreign Application Priority Data**

Jun. 20, 1995 [JP] Japan 7-153500

[51] Int. Cl.[7] C07D 401/02; A61K 31/44

[52] U.S. Cl. 514/342; 514/340; 514/369; 514/376; 546/269.7; 546/271.4; 548/183; 548/227

[58] Field of Search 546/269.7, 271.4; 548/183, 227; 514/340, 342, 369, 376

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[57] **ABSTRACT**

Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with other antidiabetics differing from the enhancer in the mechanism of action, which shows a potent depressive effect on diabetic hyperglycemia and is useful for prophylaxis and treatment of diabetes.

17 Claims, No Drawings

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PHARMACEUTICAL COMPOSITION

This is a divisional application of Ser. No. 09/057,465, filed Apr. 9, 1998, now U.S. Pat. No. 5,965,584 which was a divisional application of Ser. No. 08/667,979, filed Jun. 19, 1996, now U.S. Pat. No. 5,952,356.

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a pharmaceutical composition comprising an insulin sensitivity enhancer in combination with one or more other antidiabetics differing from said enhancer in the mechanism of action.

Recent years, the pathology of diabetes has become more and more understood and, in parallel, drugs specific for the respective pathologic states have been developed. Accordingly a variety of drugs having new mechanisms of action have appeared one after another.

Insulin sensitivity enhancers are also known as insulin resistance deblockers because they have the action to normalize the impaired insulin receptor function, and are gathering much attention in these years.

Regarding such insulin sensitivity enhancers, a very useful compound such as pioglitazone has been developed [Fujita et al., Diabetes, 32, 804–810, 1983, JP-A S55(1980)-22636 (EP-A 8203), JP-A S61(1986)-267580 (EP-A 193256)]. Pioglitazone restores the impaired insulin receptor function to normalize the uneven distribution of glucose transporters in cells, the cardinal enzyme systems associated with glycometabolism, such as glucokinase, and enzyme systems associated with lipidmetabolism, such as lipoprotein lipase. As the results, insulin resistance are deblocked to improve glucose tolerance, and lower the plasma concentrations of neutral lipids and free fatty acids. Since these actions of pioglitazone are comparatively gradual and the risk of side effect in long-term administration is also low, this compound is useful for obese patients who are presumed to be highly insulin-resistant.

Also, insulin sensitivity enhancers such as CS-045, thazolidinedione derivatives and substituted thiazolidinedione derivatives are reported to be used in combination with insulin [JP-A H4(1992)-66579, JP-A H4(1992)-69383, JP-A H5(1993)-202042]. However, the pharmaceutical composition having a specific combination of the present invention is unknown.

Diabetes is a chronic disease with diverse pathologic manifestations and is accompanied by lipidmetabolism disorders and circulatory disorders as well as glycometabolism disorders. As the results, diabetes tends to progress entailing various complications in many cases. Therefore, it is necessary to select the drug of choice for the prevailing disease state in each individual case. However, this selection is often difficult in clinical settings because single use of each individual drug can not bring sufficient effects in some disease states and there are various problems such as side effect which is caused by an increased dose or a long-term administration.

SUMMARY OF THE INVENTION

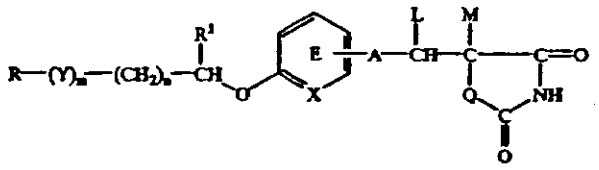
In view of the above state of the art, the inventors of the present invention did much research to develop antidiabetics which would not virtually cause adverse reactions even on long-term administration and could be effective for a large cohort of the diabetic population. As a consequence, they discovered that the above object can be accomplished by using an insulin sensitivity enhancer, such as the drug described above, in combination with other antidiabetics differing from said enhancer in the mechanism of action, and accordingly have perfected the present invention.

The present invention, therefore, relates to:

1) Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with at least one member of the group consisting of an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor;

2) Pharmaceutical composition according to 1), wherein the insulin sensitivity enhancer is a compound represented by the formula:

(I)



wherein R represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR³— (wherein R³ represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R¹ represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 substituents, and the substituents may optionally be combined with R¹ to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; or a pharmacologically acceptable salt thereof;

3) Pharmaceutical composition according to 2), wherein the compound represented by the formula (I) is pioglitazone;

4) Pharmaceutical composition according to 1), which comprises an insulin sensitivity enhancer in combination with an α-glucosidase inhibitor;

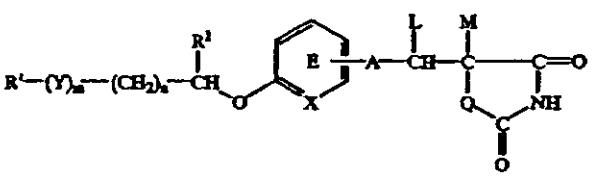
5) Pharmaceutical composition according to 4), wherein the α-glucosidase inhibitor is voglibose;

6) Pharmaceutical composition according to 4), wherein the insulin sensitivity enhancer is pioglitazone and the α-glucosidase inhibitor is voglibose;

7) Pharmaceutical composition according to 1), which is for prophylaxis or treatment of diabetes;

8) Pharmaceutical composition which comprises a compound represented by the formula:

(II)

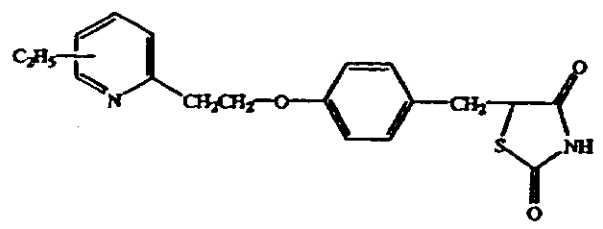


wherein R' represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR³— (wherein R³ represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen

atom or sulfur atom; R^2 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 substituents, and the substituents may optionally be combined with R^2 to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; with a proviso that R' does not represent benzopyranyl group when m and n are O, X represents CH, A represents a bond, Q represents sulfur atom, R^3, L and M represent hydrogen atom and ring E does not have further substituents; or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation;

9) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is the compound represented by the formula:

(III)



10) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is pioglitazone;

11) Pharmaceutical composition according to 8), wherein the insulin secretion enhancer is glibenclamide;

12) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is pioglitazone and the insulin secretion enhancer is glibenclamide;

13) Pharmaceutical composition according to 8), which is for prophylaxis or treatment of diabetes.

DETAILED DESCRIPTION OF THE INVENTION

The term "insulin sensitivity enhancer" as used in this specification means any and all drug substances that restore the impaired insulin receptor function to deblock insulin resistance and consequently enhance insulin sensitivity. As examples of the insulin sensitivity enhancer, the compound represented by the formula (I) or a pharmacologically acceptable salt thereof can be mentioned.

In the formula (I), as the hydrocarbon group in the optionally substituted hydrocarbon group represented by R, mention is made of aliphatic hydrocarbon groups, alicyclic hydrocarbon groups, alicyclic-aliphatic hydrocarbon groups, aromatic aliphatic hydrocarbon groups and aromatic hydrocarbon groups. Number of carbon atoms in these hydrocarbon groups is preferably 1 to 14.

The aliphatic hydrocarbon groups are preferably those having 1 to 8 carbon atoms. As the aliphatic hydrocarbon groups, mention is made of C_{1-8} saturated aliphatic hydrocarbon groups (e.g. alkyl group) as exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, hexyl, isohexyl, heptyl and octyl, and C_{2-8} unsaturated aliphatic hydrocarbon groups (e.g. alkenyl group, alkadienyl group, alkynyl group, alkadiynyl group) as exemplified by vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptynyl and 1-octynyl.

The alicyclic hydrocarbon groups are preferably those having 3 to 7 carbon atoms. As the alicyclic hydrocarbon groups, mention is made of C_{3-7} saturated alicyclic hydrocarbon grips (e.g. cycloalkyl group) as exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and C_{5-7} unsaturated alicyclic hydrocarbon groups (e.g. cycloalkenyl group, cycloalkadienyl group) as exemplified by 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl and 2,4-cycloheptadienyl.

As the alicyclic-aliphatic hydrocarbon groups, mention is made of, among those formed by combination of the above-mentioned alicyclic hydrocarbon groups with aliphatic hydrocarbon groups (e.g. cycloalkyl-alkyl group, cycloalkenyl-alkyl group), ones having 4 to 9 carbon atoms as exemplified by cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl and cycloheptylethyl.

The aromatic aliphatic hydrocarbon groups are preferably those having 7 to 13 carbon atoms (e.g. aralkyl group). As the aromatic aliphatic hydrocarbon groups, mention is made of C_{7-9} phenylalkyl as exemplified by benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and 1-phenylpropyl, and C_{11-13} naphthylalkyl as exemplified by α-naphthylmethyl, α-naphthylethyl, β-naphthylmethyl and β-naphthylethyl.

As the aromatic hydrocarbon groups, mention is made of, ones having 6 to 14 carbon atoms as exemplified by phenyl, naphthyl (α-naphtyl, β-naphthyl).

In the formula (I), as the heterocyclic group in the optionally substituted heterocyclic group represented by R, mention is made of, for example, 5- to 7-membered heterocyclic groups containing, as a ring component atom, 1 to 4 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom, and a condensed ring group. As the condensed ring, mention is made of, for example, these 5- to 7-membered heterocyclic groups condensed with 6-membered ring containing one or two nitrogen atoms, benzene ring or 5-membered ring containing one sulfur atom.

Examples of these heterocyclic groups include 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, 1 H-indazol-3-yl, 1 H-pyrrolo[2,3-b]pyrazin-2-yl, 1 H-pyrrolo[2,3-b]pyridin-6-yl, 1 H-imidazo[4,5-b]pyridin-2-yl, 1 H-imidazo[4,5-c]pyridin-2-yl, 1 H-imidazo[4,5-b]pyrazin-2-yl and benzopyranyl. Among them, pyridyl, oxazolyl or thiazolyl group is preferable.

In the formula (I), the hydrocarbon group and heterocyclic group represented by R may optionally have 1 to 5, preferably 1 to 3 substituents at any substitutable positions.

Examples of such substituents include aliphatic hydrocarbon group, alicyclic hydrocarbon group, aryl group, aromatic heterocyclic group, non-aromatic heterocyclic group, halogen atom, nitro group, optionally substituted amino group, optionally substituted acyl group, optionally substituted hydroxyl group, optionally substituted thiol group, optionally esterified carboxyl group, amidino group, carbamoyl group, sulfamoyl group, sulfo group, cyano group, azido group and nitroso group.

Examples of the aliphatic hydrocarbon groups include C_{1-15} straight-chain or branched aliphatic hydrocarbon groups as exemplified by alkyl group, alkenyl group, and alkynyl group.

Preferable examples of the alkyl group include C_{1-10} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, hexyl, pentyl, octyl, nonyl and decyl.

Preferable examples of the alkenyl group include C_{2-10} alkenyl groups such as vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl.

Preferable examples of the alkynyl group include C_{2-10} alkynyl groups such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As the alicyclic hydrocarbon group, mention is made of C_{3-12} saturated or unsaturated alicyclic hydrocarbon groups as exemplified by cycloalkyl group, cycloalkenyl group and cycloalkadienyl group.

Preferable examples of cycloalkyl group include C_{3-10} cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl and bicyclo[4.3.1]decyl.

Preferable examples of the cycloalkenyl group include C_{3-10} cycloalkenyl groups such as 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl and 3-cyclohexen-1-yl.

Preferable examples of the cycloalkadienyl group include C_{4-10} cycloalkadienyl groups such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl and 2,5-cyclohexadien-1-yl.

Preferable examples of the aryl group include C_{6-14} aryl groups such as phenyl, naphthyl (1-naphthyl, 2-naphthyl), anthryl, phenanthryl and acenaphthylenyl.

Preferable examples of the aromatic heterocyclic group include aromatic monocyclic heterocyclic groups such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl; and aromatic condensed heterocyclic groups such as benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1 H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, 1,2-benzoisothiazolyl, 1 H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylidinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenathridinyl, phenathrolinyl, idolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl.

Preferable examples of the non-aromatic heterocyclic group include oxiranyl, azetidinyl, oxethanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidino, piperidino, morpholino and thiomorpholino.

Examples of the halogen atom include fluorine, chlorine, bromine and iodine.

As the substituted amino group in the optionally substituted amino group, mention is made of, N-monosubstituted amino group and N,N-disubstituted amino group. Examples of the substituted amino groups include amino groups having one or two substituents selected from C_{1-10} alkyl group, C_{2-10} alkenyl group, C_{2-10} alkynyl group, aromatic group, heterocyclic group and C_{1-10} acyl group (e.g. methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclohexylamino, phenylamino, N-methyl-N-phenyl-amino, acetylamino, propionylamino, benzoylamino and nicotinoylamino).

As the acyl group, mention is made of C_{1-13} acyl groups such as C_{1-10} alkanoyl group, C_{3-10} alkenoyl group, C_{4-10} cycloalkanoyl group, C_{4-10} cycloalkenoyl group and C_{6-12} aromatic carbonyl group.

Preferable examples of the C_{1-10} alkanoyl group include formyl acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl and octanoyl. Preferable examples of the C_{3-10} alkenoyl group include acryloyl, methacryloyl, crotonoyl and isocrotonoyl. Preferable examples of C_{4-10} cycloalkanoyl group include cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl and cycloheptanecarbonyl. Preferable examples of C_{4-10} cycloalkenoyl group include 2-cyclohexenecarbonyl. Preferable examples of C_{6-12} aromatic carbonyl group include benzoyl, naphthoyl and nicotinoyl.

As the substituent in the substituted acyl group, mention is made of, for example, C_{1-3} alkyl group, C_{1-3} alkoxy group, halogen atom (e.g. chlorine, -fluorine, bromine, etc.), nitro group, hydroxyl group and amino group.

As the substituted hydroxyl group in the optionally substituted hydroxyl group, mention is made of, for example, alkoxy group, cycloalkyloxy group, alkenyloxy group, cycloalkenyloxy group, aralkyloxy group, acyloxy group and aryloxy group.

Preferable examples of the alkoxy group include C_{1-10} alkoxy groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, t.-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy and nonyloxy. Preferable examples of the cycloalkyloxy group include C_{3-10} cycloalkyloxy groups such as cyclobutoxy, cyclopentyloxy and cyclohexyloxy. Preferable examples of the alkenyloxy group include C_{2-10} alkenyloxy groups such as allyloxy, crotyloxy, 2-pentenyloxy and 3-hexenyloxy. Preferable examples of the cycloalkenyloxy group include C_{3-10} cycloalkenyloxy groups such as 2-cyclopentenyloxy and 2-cyclohexenyloxy. Preferable examples of the aralkyloxy group include C_{7-10} aryloxy groups such as phenyl-C_{1-4} alkyloxy (e.g. benzyloxy and phenethyloxy). Preferable examples of the acyloxy group

include C_{2-13} acyloxy group, more preferably C_{2-4} alkanoyloxy groups (e.g. acetyloxy, propionyloxy, butyryloxy and isobutyryloxy). Preferable examples of the aryloxy group include C_{6-14} aryloxy groups such as phenoxy and naphthyloxy. The aryloxy group may optionally have one or two substituents such as halogen atom (e.g. chlorine, fluorine, bromine). Examples of the substituted aryloxy group include 4-chlorophenoxy.

As the substituted thiol group in the optionally substituted thiol group, mention is made of, alkylthio group, cycloalkylthio group, alkenylthio group, cycloalkenylthio group, aralkylthio group, acylthio group and arylthio group.

Preferable examples of the alkylthio group include C_{1-10} alkylthio groups such as methylthio, ehtylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec.-butylthio, t.-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio and nonylthio. Preferable examples of the cycloalkylthio group include C_{3-10} cycloalkylthio groups such as cyclobutylthio, cyclopentylthio and cyclohexylthio. Preferable examples of the alkenylthio group include C_{2-10} alkenylthio groups such as allylthio, crotylthio, 2-pentenylthio and 3-hexenylthio. Preferable examples of the cycloalkenylthio group include C_{3-10} cycloalkenylthio groups such as 2-cyclopentenylthio and 2-cyclohexenylthio. Preferable examples of the aralkylthio include C_{7-10} aralkylthio groups such as phenyl-C_{1-4}alkylthio (e.g. benzylthio and phenethylthio). Preferable examples of the acylthio group include C_{2-13} acylthio group, more preferably C_{2-4} alkanoylthio groups (e.g. acetylthio, propionylthio, butyrylthio and isobutyrylthio).

Preferable examples of the arylthio group include C_{6-14} arylthio groups such as phenylthio and naphthylthio. The arylthio group may optionally have one or two substituents such as halogen atom (e.g. chlorine, fluorine, bromine). Examples of the substituted arylthio group include 4-chlorophenylthio.

As the optionally esterified carboxyl group, mention is made of, for example, alkoxycarbonyl group, aralkyloxycarbonyl group and aryloxycarbonyl group.

Preferable examples of the alkoxycarbonyl group include C_{2-5} alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and butoxycarbonyl. Preferable examples of the aralkyloxycarbonyl group include C_{8-10} aralkyloxycarbonyl groups such as benzyloxycarbonyl. Preferable examples of the aryloxycarbonyl group include C_{7-15} aryloxycarbonyl groups such as phenoxycarbonyl and p-tolyloxycarbonyl.

Among the substituents on the hydrocarbon group and heterocyclic group represented by R, C_{1-10} alkyl groups, aromatic heterocyclic groups and C_{6-14} aryl groups are preferable, and C_{1-3} alkyl, furyl, thienyl, phenyl and naphthyl are especially preferable.

In the formula (I), substituents on the hydrocarbon group and heterocyclic group which are represented by R, may, when they are alicyclic hydrocarbon group, aryl group, aromatic heterocyclic group or non-aromatic heterocyclic group, have one or more, preferably 1 to 3, of suitable substituents respectively. Examples of these substituents include C_{1-6} alkyl groups, C_{2-6} alkenyl groups, C_{2-6} alkynyl groups, C_{3-7} cycloalkyl groups, C_{6-14} aryl groups, aromatic heterocyclic groups (e.g. thienyl, furyl, pyridyl, oxazolyl and thiazolyl), non-aromatic heterocyclic groups (e.g. tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolidino and piperazino), C_{7-9} aralkyl groups, amino group, N-mono-C_{1-4} alkylamino groups, N,N-di-C_{1-4} alkylamino groups, C_{2-8} acylamino groups (e.g. acetylamino, propionylamino and benzoylamino), amidino group, C_{2-8} acyl group (e.g. C_{2-8} alkanoyl groups), carbamoyl group, N-mono-C_{1-4} alkyl carbamoyl groups, N,N-di-C_{1-4} alkyl carbamoyl groups, sulfamoyl group, N-mono-C_{1-4} alkyl sulfamoyl groups, N,N-di-C_{1-4} alkyl sulfamoyl groups, carboxyl group, C_{2-8} alkoxycarbonyl groups, hydroxyl group, C_{1-4} alkoxy groups, C_{2-5} alkenyloxy groups, C_{3-7} cycloalkyloxy groups, C_{7-9} aralkyloxy groups, C_{6-14} aryloxy groups, mercapto group, C_{1-4} alkylthio groups, C_{7-9} aralkylthio groups C_{6-14} arylthio groups, sulfo group, cyano group, azido group, nitro group, nitroso group and halogen atom.

In formula (I), R is preferably an optionally substituted heterocyclic group. R is more preferably pyridyl, oxazolyl or thiazolyl group which is optionally substituted by 1 to 3 substituents selected from C_{1-3} alkyl group, furyl group, thienyl group, phenyl group and naphthyl group.

R' in the formula (II) has the same definition as R except that R' does not represent benzopyranyl group when m and n are 0; X represents CH; A represents a bond; Q represents sulfur atom; R^1, L and M represent hydrogen atom; and ring E does not have further substituents.

In the formulae (I) and (II), Y represents —CO—, —CH(OH)— or —NR^3— (wherein R^3 represents an optionally substituted alkyl group), preferably —CH(OH)— or —NR^3—. As the alkyl group in the optionally substituted alkyl group represented by R^3, mention is made of, for example, C_{1-4} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl and t.-butyl. Examples of the substituents include halogen (e.g., fluorine, chlorine, bromine and iodine), C_{1-4} alkoxy groups (e.g. methoxy, ethoxy, propoxy, butoxy, isobutoxy, sec.-butoxy and t.-butoxy), hydroxyl group, nitro group and C_{1-4} acyl groups (e.g. formyl, acetyl and propionyl).

The symbol m is 0 or 1, preferably 0.

The symbol n is 0, 1 or 2, preferably 0 or 1.

X represents CH or N, preferably CH.

In the formula (I) and (II), A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group. The aliphatic hydrocarbon group may be straight-chain or branched, and saturated or unsaturated. Specific examples of the aliphatic hydrocarbon group include saturated ones [e.g. —CH_2—, —$CH(CH_3)$—, —$(CH_2)_2$—, —$CH(C_2H_5)$—, —$(CH_2)_3$—, —$(CH_2)_4$—, —$(CH_2)_5$—, —$(CH_2)_6$— and —$(CH_2)_7$—] and unsaturated ones [e.g. —CH=CH—, —$C(CH_3)$=CH—, —CH=CH—CH_2—, —$C(C_2H_5)$=CH—, —CH_2—CH=CH—CH_2—, —CH_2—CH_2—CH=CH—CH_2—, —CH=CH—CH=CH—CH_2— and —CH=CH—CH=CH—CH=CH—CH_2—. A is preferably a bond or C_{1-4} divalent aliphatic hydrocarbon groups, the aliphatic hydrocarbon groups preferably being saturated. A is more preferably a bond or —$(CH_2)_2$—.

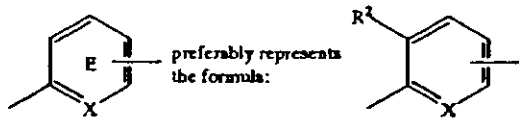
As the alkyl group represented by R^1, substantially the same one as the alkyl group in the above-mentioned R^3. R^1 is preferably hydrogen atom.

In the formulae (I) and (II), the partial formula:

Ring E has 1 to 4 substituents at any substitutable positions. Examples of such substituents include alkyl group,

optionally substituted hydroxyl group, halogen atom, optionally substituted acyl group and optionally substituted amino group. These substituents have substantially the same meaning as those described as substituents of the hydrocarbon group and heterocyclic group represented by R.

Ring E, namely the partial formula:



wherein R^2 represents hydrogen atom, an alkyl group, an optionally substituted hydroxyl group, a halogen atom, an optionally substituted acyl group, nitro group or an optionally substituted amino group.

As the alkyl group, optionally substituted hydroxyl group, halogen atom, optionally substituted acyl group and optionally substituted amino group represented by R^2, mention is made of those described as substituents of the hydrocarbon group and heterocyclic group represented by R. R^2 is preferably hydrogen atom, optionally substituted hydroxyl group or halogen atom, more preferably hydrogen atom or optionally substituted hydroxyl group, especially preferably hydrogen atom or C_{1-4} alkoxy groups.

In the formula (I) and (II), L and M represent hydrogen atom, or they may optionally be combined with each other to form a bond. L and M are preferably hydrogen atom.

In the compounds wherein L and M are combined with each other to form a bond, there exist (E)— and (Z)— isomers relative to the double bond at the 5-position of the azolidinedione ring.

And, in the compounds wherein L and M respectively represent hydrogen atom, there exist (R)— and (S)— optical isomers due to the asymmetric carbon at the 5-position of the azolidinedione ring. The compounds include these (R)— and (S)— optical isomers and racemic isomers.

Preferable examples of the compounds represented by the formula (I) or (II) includes those in which R is pyridyl, oxazolyl or thiazolyl group optionally having 1 to 3 substituents selected from C_{1-3} alkyl, furyl, thienyl, phenyl and naphthyl; m is 0; n is 0 or 1; X is CH; A is a bond or $—(CH_2)_2—$; R^1 is hydrogen atom; ring E, namely the partial formula:

and R^2 is hydrogen atom or C_{1-4} alkoxy group; and L and M are both hydrogen atom.

Preferable examples of the compound represented by the formula (I) include

(1) the compound represented by the formula (III) such as 5-[4-[2-(3-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione; 5-[4-[2-(4-ethyl-2-pyridyl)ethoxy]-benzyl]-2,4-thiazolidinedione; 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (generic name: pioglitazone); and 5-[4-[2-(6-ethyl-2-pyridyl)-ethoxy]benzyl]-2,4-thiazolidinedione;

(2) (R)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione; and

(3) 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2 H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (generic name: troglitazone/CS-045).

The compound represented by the formula (I) is especially preferably pioglitazone.

The compound represented by the formula (II) is preferably the compound represented by the formula (III) and (R)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione, more preferably pioglitazone.

The pharmacologically acceptable salt of the compound represented by the formula (I) or (II) are exemplified by salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

Preferable examples of salts with inorganic bases include salts with alkali metals such as sodium, potassium, etc., salts with alkaline earth metals such as calcium, magnesium, etc., and salts with aluminum, ammonium, etc.

Preferable examples of salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, etc.

Preferable examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.

Preferable examples of salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.

Preferable examples of salts with basic amino acids include salts with arginine, lysine, ornithine, etc., and preferable examples of salts with acidic amino acids include salts with aspartic acid, glutamic acid, etc.

The pharmacologically acceptable salt of the compound represented by the formula (III) is preferably a salt with an inorganic acid, more preferably a salt with hydrochloric acid. Especially, pioglitazone is preferably used in the form of salt with hydrochloric acid.

The compounds represented by the formula (I) or (II) or a salt thereof can be produced in accordance with, for example, methods described in JPA S55(1980)-22636(EP-A 8203), JPA S60(1985)-208980(EP-A 155845), JPA S61 (1986)-286376(EP-A 208420), JPA S61(1986)-85372(EP-A 177353), JPA S61(1986)-267580(EP-A 193256), JPA H5(1993)-86057(WO 92/18501), JPA H7(1995)-82269 (EP-A 605228), JPA H7(1995)-101945(EP-A 612743), EP-A 643050, EP-A 710659, etc. or methods analogous thereto.

Insulin sensitivity enhancers include 5-[[3,4-dihydro-2-(phenylmethyl)-2 H-1-benzopyran-6-yl]methyl]-2,4-thiazolidinedione (generic name: englitazone) or its sodium salt;

5-[[4-[3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl] phenyl]methyl]-2,4-thiazolidinedione (generic name: darglitazone/CP-86325) or its sodium salt;

5-[2-(5-methyl-2-phenyl-4-oxazolylmethyl)benzofuran-5-ylmethyl]-2,4-oxazolidinedione (CP-92768);

5-(2-naphthalenylsulfonyl)-2,4-thiazolidinedione (AY-31637);

4-[(2-naphthalenyl)methyl]-3 H-1,2,3,5-oxathiadiazol-2-oxide (AY-30711); and

5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]-methyl]-2,4-thiazolidinedione (BRL-49653), etc. in addition to compounds mentioned hereinbefore.

In the present invention, examples of the drug which is used in combination with the above-mentioned insulin sensitivity enhancer include an α-glucosidase inhibitor, an

aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor.

α-Glucosidase inhibitors are drugs which inhibit digestive enzymes such as amylase, maltase, α-dextrinase, sucrase, etc. to retard digestion of starch and sugars. Examples of the α-glucosidase inhibitors include acarbose, N-(1,3-dihydroxy-2-propyl)valiolamine (generic name; voglibose), miglitol, etc. with preferance given to voglibose.

Aldose reductase inhibitors are drugs which inhibit the first-stage rate-limiting enzyme in the polyol pathway to prevent or arrest diabetic complications. In the hyperglycemic state of diabetes, the utilization of glucose in the polyol pathway is increased and the excess sorbitol accumulated intracellularly as a consequence acts as a tissue toxin and hence evokes the onset of complications such as diabetic neuropathy, retinopathy, and nephropathy. Examples of the aldose reductase inhibitors include tolurestat; epalrestat; 3,4-dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxazine-4-acetic acid; 2,7-difluoro-spiro(9H-fluorene-9,4'-imidazolidine)-2',5'-dione (generic name: imirestat); 3-[(4-bromo-2-fluorophenyl)methyl]-7-chloro-3,4-dihydro-2,4-dioxo-1(2H)-quinazoline acetic acid (generic name: zenarestat); 6-fluoro-2,3-dihydro-2',5'dioxo-spiro[4H-1-benzopyran-4,4'-imidazolidine]-2-carboxamide (SNK-860); zopolrestat; sorbinil; and 1-[(3-bromo-2-benzofuranyl) sulfonyl]-2,4-imidazolidinedione (M-16209), etc.

Biguanides are drugs having actions of stimulation of anaerobic glycolysis, increase of the sensitivity to insulin in the peripheral tissues, inhibition of glucose absorption from the intestine, suppression of hepatic gluconeogenesis, and inhibition of fatty acid oxidation. Examples of the biguanides include phenformin, metformin, buformin etc.

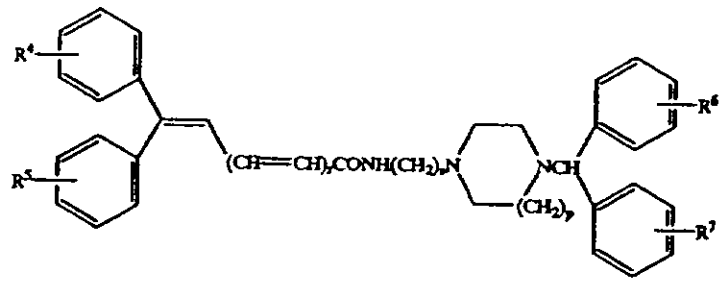
Statin compounds are drugs having actions of lowering blood cholesterol levels by inhibiting hydroxymethylglutalyl CoA (HMG-CoA) reductase. Examples of the static compounds include pravastatin and its sodium salt, simvastatin, lovastatin, atorvastatin, fluvastatin, etc.

Squalene synthesis inhibitors are drugs having actions of lowering blood cholesterol levels by inhibiting synthesis of squalene. Examples of the squalene synthesis inhibitors include (−S)-α-[Bis[2,2-dimethyl-1-oxopropoxy)methoxy] phosphinyl]-3-phenoxybenzenebutanesulfonic acid, mono potassium salt (BMS-188494).

Fibrate compounds are drugs having actions of lowering blood cholesterol levels by inhibiting synthesis and secretion of triglycerides in liver and activating a lipoprotein lipase. Examples of the fibrate compounds include bezafibrate, beclobrate, binifibrate, ciplofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrae, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate, etc.

LDL catabolism enhancers are drugs having actions of lowering blood cholesterol levels by increasing the number of LDL (low-density lipoprotein) receptors.

Examples of the LDL catabolism enhancers include the compound which is described in JPA H7(1995)-316144, and represented by the formula:



wherein R^4, R^5, R^6 and R^7 are the same or different, and represent hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group; r is 0–2; s is 2–4; p is 1–2; or a salt thereof; specifically N-[2-[4-bis(4-fluorophenyl) methyl-1-piperazinyl]ethyl]-7,7-diphenyl-2,4,6-heptatrienic acid amide, etc.

The above-mentioned statin compounds, squalene synthesis inhibitors, fibrate compounds and LDL catabolism enhancers can be substituted with other drugs having the property to lower blood cholesterol and triglyceride levels. Examples of these drugs include nicotinic acid derivatives such as nicomol and niceritrol; antioxidants such as probucol; and ion-exchange resins such as colestyramin.

Angiotensin converting enzyme inhibitors are drugs having actions of partially lowering blood glucose levels as well as lowering blood pressure by inhibiting angiotensin converting enzymes. Examples of the angiotensin converting enzyme inhibitors include captopril, enalapril, alacepril, delapril, ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moveltopril, perindopril, quinapril, spirapril, temocapril, trandolapril, etc.

In the present invention, especially preferred is the pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with an α-glucosidase inhibitor. The insulin sensitivity enhancer is especially preferably pioglitazone, and the α-glucosidase inhibitor is especially preferably voglibose.

In the present invention, examples of the drug which is used in combination with the compound represented by the formula (II) or a pharmacologically acceptable salt thereof include an insulin secretion enhancer and/or an insulin preparation.

Insulin secretion enhancers are drugs having the property to promote secretion of insulin from pancreatic β cells. Examples of the insulin secretion enhancers include sulfonylureas (SU). The sulfonylureas (SU)are drugs which promote secretion of insulin from pancreatic β cells by transmitting signals of insulin secretion via SU receptors in the cell membranes. Examples of the SU include tolbutamide; chlorpropamide; tolazamide; acetohexamide; 4-chloro-N-[(1-pyrolidinylamino)carbonyl]-benzenesulfonamide (generic name: glycopyramide) or its ammonium salt; glibenclamide (glyburide); gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; tolcyclamide, etc.

Insulin secretion enhancers include N-[[4-(1-methylethyl) cyclohexyl)carbonyl]-D-phenylalanine (AY-4166); calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl) propionate dihydrate (KAD-1229); and glimepiride (Hoe 490), etc. in addition to compounds mentioned hereinbefore. The insulin secretion enhancer is especially preferably glibenclamide.

Examples of the insulin preparations include animal insulin preparations typically extracted from bovine or procine pancreas and human insulin preparations synthesized by genetic engineering techniques typically using *Escherichia coli* or yeasts. While insulin preparations are available in a variety of types, e.g. immediate-acting, bimodal-acting intermediate-acting, and long-acting, these types of preparations can be selectively administered according to the patient's condition.

In the present invention, especially preferred is the pharmaceutical composition which comprises the compound represented by the formula (II) or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer. The compound represented by the formula (II) or a pharmacologically acceptable salt thereof is especially preferably pioglitazone, and the insulin secretion enhancer is especially preferably glibenclamide.

The pharmaceutical composition comprising an insulin sensitivity enhancer in combination with at least one member selected from the group consisting of an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor; and the pharmaceutical composition comprising the compound represented by the formula (II) or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation, both provided in accordance with the present invention, can be respectively put to use by mixing the respective active components either all together or independently with a physiologically acceptable carrier, excipient, binder, diluent, etc. and administering the mixture or mixtures either orally or non-orally as a pharmaceutical composition. When the active components are formulated independently, the respective formulations can be extemporaneously admixed using a diluent or the like and administered or can be administered independently of each other, either concurrently or at staggered times to the same subject.

The dosage form for said pharmaceutical composition includes such oral dosage forms as granules, powders, tablets, capsules, syrups, emulsions, suspensions, etc. and such non-oral dosage forms as injections (e.g. subcutaneous, intravenous, intramuscular and intraperitoneal injections), drip infusions, external application forms (e.g. nasal spray preparations, transdermal preparations ointments, etc.), and suppositories (e.g. rectal and vaginal suppositories).

These dosage forms can be manufactured by the per se known technique conventionally used in pharmaceutical procedures. The specific manufacturing procedures are as follows.

To manufacture an oral dosage form, an excipient (e.g. lactose, sucrose, starch, mannitol, etc.), a disintegrator (e.g. calcium carbonate, carboxymethylcellulose calcium, etc.), a binder (e.g. α-starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, etc.), and a lubricant (e.g. talc, magnesium stearate, polyethylene glycol 6000, etc.), for instance, are added to the active component or components and the resulting composition is compressed. Where necessary, the compressed product is coated, by the per se known technique, for masking the taste or for enteric dissolution or sustained release. The coating material that can be used includes, for instance, ethylcellulose, hydroxymethylcellulose, polyoxyethylene glycol, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, and Eudragit (Rohm & Haas, Germany, methacrylic-acrylic copolymer).

Injections can be manufactured typically by the following procedure. The active component or components are dissolved, suspended or emulsified in an aqueous vehicle (e.g. distilled water, physiological saline, Ringer's solution, etc.) or an oily vehicle (e.g. vegetable oil such as olive oil, sesame oil, cottonseed oil, corn oil, etc. or propylene glycol) together with a dispersant (e.g. Tween 80 (Atlas Powder, U.S.A.), HCO 60 (Nikko Chemicals), polyethylene glycol, carboxymethylcellulose, sodium alginate, etc.), a preservative (e.g. methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, benzyl alcohol, chlorobutanol, phenol, etc.), an isotonizing agent (e.g. sodium chloride, glycerol, sorbitol, glucose, inverted sugar, etc.) and other additives. If desired, a solubilizer (e.g. sodium salicylate, sodium acetate, etc.), a stabilizer (e.g. human serum albumin), a soothing agent (e.g. benzalkoxium chloride, procaine hydrochloride, etc.) and other additives can also be added.

A dosage form for external application can be manufactured by processing the active component or components into a solid, semi-solid or liquid composition. To manufacture a solid compositions, for instance, the active component or components, either as they are or in admixture with an excipient (e.g. lactose, manmitol, starch, microcrystalline cellulose, sucrose, etc.), a thickener (e.g. natural gums, cellulose derivatives, acrylic polymers, etc.), etc., are processed into powders. The liquid composition can be manufactured in substantially the same manner as the injections mentioned above. The semi-solid composition is preferably provided in a hydrous or oily gel form or an ointment form. These compositions may optionally contain a pH control agent (e.g. carbonic acid, phosphoric acid, citric acid, hydrochloric acid, sodium hydroxide, etc.), and a preservative (e.g. p-hydroxybenzoic acid esters, chlorobutanol, benzalkonium chloride, etc.), among other additives.

Suppositories can be manufactured by processing the active component or components into an oily or aqueous composition, whether solid, semi-solid or liquid. The oleaginous base that can be used includes, for instance, higher fatty acid glycerides [e.g. cacao butter, Witepsols (Dinamit-Nobel), etc.], medium-chain fatty acids [e.g. Migriols (Dinamit-Nobel), etc.], vegetable oils (e.g. sesame oil, soybean oil, cottonseed oil, etc.), etc. The water-soluble base includes, for instance, polyethylene glycols, propylene glycol, etc. The hydrophilic base includes, for instance, natural gums, cellulose derivatives, vinyl polymers, and acrylic polymers, etc.

The pharmaceutical composition of the present intention is low in toxicity and can be safely used in mammals (e.g. humans, mice, rats, rabbits, dogs, cats, bovines, horses, swines, monkeys).

The dosage of the pharmaceutical composition of the present invention may be appropriately determined with reference to the dosages recommended for the respective active components and can be selected appropriately according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of the active components, among other factors. For example, the dosage of the insulin sensitivity enhancer for an adult can be selected from the clinical oral dose range of 0.01 to 10 mg/kg body weight (preferably 0.05 to 10 mg/kg body

weight, more preferably 0.05 to 5 mg/kg body weight) or the clinical parenteral dose range of 0.005 to 10 mg/kg body weight (preferably 0.01 to 10 mg/kg body weight, more preferably 0.01 to 1 mg/kg body weight). The other active component or components having different modes of action for use in combination can also be used in dose ranges selected by referring to the respective recommended clinical dose ranges. The preferred frequency of administration is 1 to 3 times a day.

The proportions of the active components in the pharmaceutical composition of the present invention can be appropriately selected according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of active components, among other factors. When, for example, the compound represented by the formula (I) or a pharmacologically acceptable salt thereof (e.g. pioglitazone) which is the insulin sensitivity enhancer and voglibose which is an α-glucosidase inhibitor are to be administered in combination to a human subject, voglibose is used in a proportion of usually about 0.001 to 0.2 weight parts and preferably about 0.001 to 0.02 weight parts relative to 1 weight part of the compound or a salt thereof. When, for example, the compound represented by the formula (II) or a pharmacologically acceptable salt thereof and glibenclamide which is an insulin secretion enhancer are to be administered in combination to a human subject, glibenclamide is used in a proportion of usually about 0.002 to 5 weight parts and preferably about 0.025 to 0.5 weight parts, relative to 1 weight part of the compound or a pharmacologically acceptable salt thereof.

The pharmaceutical composition of the present invention shows a marked synergistic effect compared with administration of either active component alone. For example, compared with cases in which each of these active components was administered to diabetic Wistar fatty rats with genetical obesity, administration of these active component sin combination resulted in marked improvements in both hyperglycemia and reduced glucose tolerance. Thus, the pharmaceutical composition of the present invention lowers blood glucose in diabetics more effectively than it is the case with administration of each component drug along and, therefore, can be used advantageously for the prophylaxis and treatment of diabetic complications.

Furthermore, since the pharmaceutical composition of the present invention develops sufficient efficacy with reduced doses as compared with the administration of any one of the active components along, the side effects of the respective components (e.g. gastrointestinal disorders such as diarrhea, etc.) can be reduced.

The following working examples and experimental examples are merely intended to illustrate the present invention in further detail but should by no means be construed as defining the scope of the invention.

The pharmaceutical composition of the present invention can be prepared according to the following formulations.

WORKING EXAMPLE 1

Capsules	
(1) Pioglitazone hydrochloride	30 mg
(2) Voglibose	0.2 mg
(3) Lactose	60 mg
(4) Microcrystalline cellulose	79.8 mg
(5) Magnesium stearate	10 mg
Total	180 mg

The whole amounts of (1), (2), (3) and (4) and half the amount of (5) are mixed well and granulated in the conventional manner. Then, the balance of (5) is added and, after mixing, the whole composition is filled in a gelatin hard capsule shell.

WORKING EXAMPLE 2

Tablets	
(1) Pioglitazone hydrochloride	10 mg
(2) Glibenclamide	1.25 mg
(3) Lactose	86.25 mg
(4) Corn starch	20 mg
(5) Polyethylene glycol	2.5 mg
(6) Hydroxypropylcellulose	4 mg
(7) Carmellose calcium	5.5 mg
(8) Magnesium stearate	0.5 mg
	130 mg (per tablet)

The whole amounts of (1), (2), (3), (4), and (5), ⅔ amounts of (6) and (7), and ½ amount of (8) are mixed well and granulated in the conventional manner. Then, the balances of (6), (7) and (8) are added to the granules, which is mixed well and the whole composition is compressed with a tablet machine. The adult dosage is 3 tablets/day, to be taken in 1 to 3 divided doses.

WORKING EXAMPLE 3

Capsules	
(1) Pioglitazone hydrochloride	10 mg
(2) Epalrestat	50 mg
(3) Lactose	55 mg
(4) Microcrystalline cellulose	55 mg
(5) Magnesium stearate	10 mg
Total	180 mg

The whole amounts of (1), (2), (3) and (4) and ½ amount of (5) are mixed well and granulated in the conventional manner. Then, the balance of (5) is added and the whole composition is filled in gelatin capsule shell. The adult dosage is 3 capsules/day, to be taken in 1 to 3 divided doses.

EXPERIMENTAL EXAMPLE 1

Effect of pioglitazone hydrochloride in combination with α-glucosidase inhibitor in genetically obese and diabetic Wistar fatty rats.

Male Wistar fatty rates aged 14–19 weeks were divided into 4 groups of 5–6, and pioglitazone hydrochloride (1 mg/kg body wt./day, p.o.) and/or voglibose (an α-glucosidase inhibitor) (0.31 mg/kg body wt./day; administered by mixing in commercial diet at a rate of 5 ppm) was administered for 14 days. The blood was then collected from the tail vein and the plasma glucose and hemoglobin A_1 were

determined by the enzymatic method (Encore Chemical System, Baker) and using a commercial kit (NC-ROPET, Nippon Chemiphar Co.), respectively. The results were expressed in mean±standard deviation for each group (n=5–6) and analyzed by Dunnett's test, which are shown in Table 1. The 1% level of significance was used.

TABLE 1

Group	Plasma glucose (mg/dl)	Hemoglobin A_1 (%)
Control	345 ± 29	5.7 ± 0.4
Pioglitazone	215 ± 50*	5.2 ± 0.3
Voglibose	326 ± 46	6.0 ± 0.6
Pioglitazone + voglibose	114 ± 23*	4.5 ± 0.4*

*P < 0.01 vs. control group

It is apparent from Table 1 that both the blood glucose and hemoglobin A_1 levels were remarkably lowered by combined administration of pioglitazone and voglibose as compared with the administration of either drug along.

EXPERIMENTAL EXAMPLE 2

Effect of pioglitazone hydrochloride in combination with an insulin secretion enhancer in genetically obese and diabetic Wistar fatty rats.

Male Wistar fatty rats aged 13–14 weeks were divided into 4 groups of 5, and pioglitazone hydrochloride (3 mg/kg/day, p.o.) and/or glibenclamide (an insulin secretion enhancer) (3 mg/kg/day, p.o.) was administered for 7 days. Following an overnight fast, the oral glucose loading test (2 g glucose/kg/5 ml, p.o.) was carried out. Prior to glucose loading and 120 and 240 minutes after the loading, blood was collected from the tail vein and the plasma glucose was assayed by the enzymatic method (Encore Chemical System, Baker). The results were expressed in mean±SD for each group (n=5) and analyzed by Dunnett's test, which are shown in Table 2.

TABLE 2

Group	Plasma glucose (mg/dl) 0 min.	120 min.	240 min.
Control	119 ± 9	241 ± 58	137 ± 10
Pioglitazone	102 ± 12	136 ± 17*	102 ± 9*
Glibenclamide	118 ± 12	222 ± 61	106 ± 24*
Pioglitazone + glibenclamide	108 ± 3	86 ± 10*	60 ± 5*

*P < 0.01 vs. control group

It is apparent from Table 2 that the increase of blood sugar following glucose loading was remarkably inhibited by the combined administration of pioglitazone and glibenclamide as compared with the administration of either drug along.

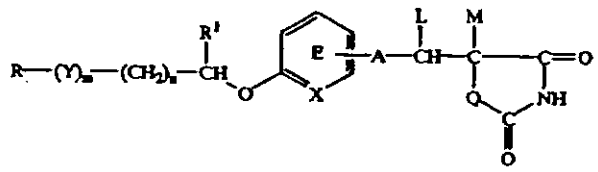
The pharmaceutical composition of the present invention shows a potent depressive effect on diabetic hyperglycemia and is useful for prophylaxis and treatment of diabetes. Moreover, this pharmaceutical composition is useful for prophylaxis and treatment of diabetic complications such as diabetic neuropathy, nephropathy, retinopathy, macroangiopathy, and osteopenia. In addition, by appropriately selecting the kinds of component drugs, administration route, dosage, etc. according to clinical status, stable hypoglycemic efficacy in long-term therapy can be expected with an extremely low risk of side effect.

What is claimed is:

1. A method for treating glycometabolism disorders in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of an insulin sensitivity enhancer in combination with a biguanide.

2. The method according to claim 1, wherein the insulin sensitivity enhancer is a compound represented by the formula:

(I)



wherein R represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR^3— wherein R^3 represents an optionally substituted alkyl group; m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R^1 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 further substituents, and the substituents may optionally be combined with R^1 to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; or a pharmacologically acceptable salt thereof.

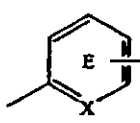
3. The method according to claim 2, wherein R is an optionally substituted heterocyclic group.

4. The method according to claim 2, wherein m is 0.

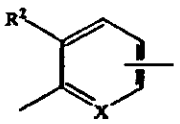
5. The method according to claim 2, wherein X is CH.

6. The method according to claim 2, wherein R^1 is hydrogen atom.

7. The method according to claim 2, wherein the partial formula:



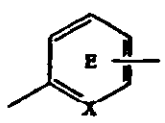
represents the formula:



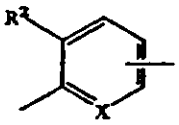
wherein R^2 represents hydrogen atom, an alkyl group, an optionally substituted hydroxyl group, a halogen atom, an optionally substituted acyl group, nitro group or an optionally substituted amino group.

8. The method according to claim 2, wherein L and M are hydrogen atoms.

9. The method according to claim 2, wherein R is pyridyl, oxazolyl or thiazolyl group optionally having 1 to 3 substituents selected from C_{1-3} alky, furyl, thienyl, phenyl and naphthyl; m is 0; n is 0 or 1; X is CH; A is a bond or —$(CH_2)_2$—; R^1 is hydrogen atom; wherein the partial formula:



represents the formula:



and wherein R^2 is hydrogen atom or C_{1-4} alkoxy group; and L and M are both hydrogen atoms.

10. The method according to claim 2, wherein the compound represented by the formula (I) is pioglitazone or its hydrochloride.

11. The method according to claim 1, wherein the biguanide is selected from the group consisting of phenformin, metformin and buformin.

12. The method according to claim 1, wherein the biguanide is metformin.

13. The method according to claim 1, wherein the insulin sensitivity enhancer is pioglitazone or its hydrochloride and the biguanide is metformin.

14. The method according to claim 1, wherein the insulin sensitivity enhancer is troglitazone.

15. The method according to claim 1, wherein the insulin sensitivity enhancer is 5-[[4-[2-(methyl-2-pyridylamino) ethoxy]phenyl]-methyl]-2,4-thiazolidinedione or its pharmacologically acceptable salt.

16. The method according to claim 1, wherein the insulin sensitivity enhancer and biguanide are mixed together to form an admixture and the admixture is administered to the mammal.

17. The method according to claim 1, wherein the insulin sensitivity enhancer and biguanide are not mixed together but are administered independently to the mammal.

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US006166043A

United States Patent [19]

Ikeda et al.

[11] Patent Number: 6,166,043

[45] Date of Patent: Dec. 26, 2000

[54] PHARMACEUTICAL COMPOSITION

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[21] Appl. No.: 09/303,492

[22] Filed: Apr. 30, 1999

Related U.S. Application Data

[62] Division of application No. 09/057,465, Apr. 9, 1998, Pat. No. 5,965,584, which is a division of application No. 08/667,979, Jun. 19, 1996, Pat. No. 5,952,356.

[30] Foreign Application Priority Data

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[51] Int. Cl.[7] A61K 31/44; A61K 31/42; A61K 31/425; C07D 401/02

[52] U.S. Cl. 514/342; 514/340; 546/269.7; 546/271.4; 548/183; 548/227

[58] Field of Search 546/269.7, 271.4; 548/183.227; 514/340, 342

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[57] ABSTRACT

Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with other antidiabetics differing from the enhancer in the mechanism of action, which shows a potent depressive effect on diabetic hyperglycemia and is useful for prophylaxis and treatment of diabetes.

17 Claims, No Drawings

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PHARMACEUTICAL COMPOSITION

This is a divisional application of Ser. No. 09/057,465, filed Apr. 9, 1998, now U.S. Pat. No. 5,965,584 which was a divisional application of Ser. No. 08/667,979, filed Jun. 19, 1996, now U.S. Pat. No. 5,952,356.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a pharmaceutical composition comprising an insulin sensitivity enhancer in combination with one or more other antidiabetics differing from said enhancer in the mechanism of action.

2. Description of Related Art

Recent years, the pathology of diabetes has become more and more understood and, in parallel, drugs specific for the respective pathologic states have been developed. Accordingly a variety of drugs having new mechanisms of action have appeared one after another.

Insulin sensitivity enhancers are also known as insulin resistance deblockers because they have the action to normalize the impaired insulin receptor function, and are gathering much attention in these years.

Regarding such insulin sensitivity enhancers, a very useful compound such as pioglitazone has been developed [Pujita et al., Diabetes, 32, 804–810, 1983, JP-A S55(1980)-22636 (EP-A 8203), JP-A S61(1986)-267580 (EP-A 193256)]. Pioglitazone restores the impaired insulin receptor function to normalize the uneven distribution of glucose transporters in cells, the cardinal enzyme systems associated with glycometabolism, such as glucokinase, and enzyme systems associated with lipidmetabolism, such as lipoprotein lipase. As the results, insulin resistance are deblocked to improve glucose tolerance, and lower the plasma concentrations of neutral lipids and free fatty acids. Since these actions of pioglitazone are comparatively gradual and the risk of side effect in long-term administration is also low, this compound is useful for obese patients who are presumed to be highly insulin-resistant.

Also, insulin sensitivity enhancers such as CS-045, thiazolidinedione derivatives and substituted thiazolidinedione derivatives are reported to be used in combination with insulin [JP-A H4(1992)-66579, JP-A H4(1992)-69383, JP-A H5(1993)-202042]. However, the pharmaceutical composition having a specific combination of the present invention is unknown.

Diabetes is a chronic disease with diverse pathologic manifestations and is accompanied by lipidmetabolism disorders and circulatory disorders as well as glycometabolism disorders. As the results, diabetes tends to progress entailing various complications in many cases. Therefore, it is necessary to select the drug of choice for the prevailing disease state in each individual case. However, this selection is often difficult in clinical settings because single use of each individual drug can not bring sufficient effects in some disease states and there are various problems such as side effect which is caused by an increased dose or a long-term administration.

SUMMARY OF THE INVENTION

In view of the above state of the art, the inventors of the present invention did much research to develop antidiabetics which would not virtually cause adverse reactions even on long-term administration and could be effective for a large cohort of the diabetic population. As a consequence, they

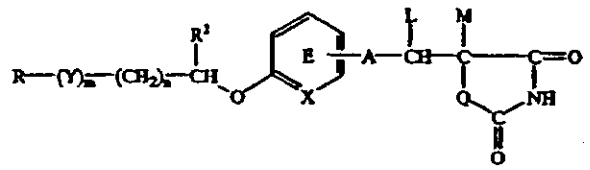
discovered that the above object can be accomplished by using an insulin sensitivity enhancer, such as the drug described above, in combination with other antidiabetics differing from said enhancer in the mechanism of action, and accordingly have perfected the present invention.

The present invention, therefore, relates to:

1) Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with at least one member of the group consisting of an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor;

2) Pharmaceutical composition according to 1), wherein the insulin sensitivity enhancer is a compound represented by the formula:

(I)



wherein R represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR^3- (wherein R^3 represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R^1 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 substituents, and the substituents may optionally be combined with R^1 to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; or a pharmacologically acceptable salt thereof;

3) Pharmaceutical composition according to 2), wherein the compound represented by the formula (I) is pioglitazone;

4) Pharmaceutical composition according to 1), which comprises an insulin sensitivity enhancer in combination with an α-glucosidase inhibitor;

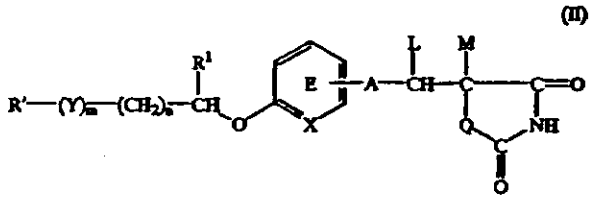
5) Pharmaceutical composition according to 4), wherein the α-glucosidase inhibitor is voglibose;

6) Pharmaceutical composition according to 4), wherein the insulin sensitivity enhancer is pioglitazone and the α-glucosidase inhibitor is voglibose;

7) Pharmaceutical composition according to 1), which is for prophylaxis or treatment of diabetes;

8) Pharmaceutical composition which comprises a compound represented by the formula:

(II)

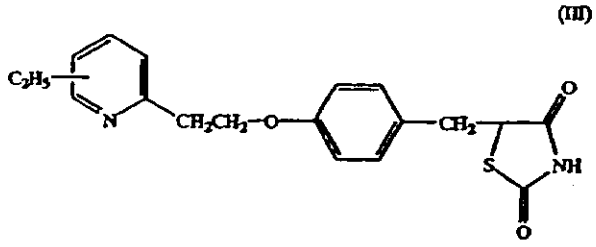


wherein R' represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR^3- (wherein R^3 represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen

atom or sulfur atom; R^2 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 substituents, and the substituents may optionally be combined with R^2 to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; with a proviso that R' does not represent benzopyranyl group when m and n are O, X represents CH, A represents a bond, Q represents sulfur atom, R^1, L and M represent hydrogen atom and ring E does not have further substituents; or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation;

9) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is the compound represented by the formula:

(III)



10) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is pioglitazone;

11) Pharmaceutical composition according to 8), wherein the insulin secretion enhancer is glibenclamide;

12) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is pioglitazone and the insulin secretion enhancer is glibenclamide;

13) Pharmaceutical composition according to 8), which is for prophylaxis or treatment of diabetes.

DETAILED DESCRIPTION OF THE INVENTION

The term "insulin sensitivity enhancer" as used in this specification means any and all drug substances that restore the impaired insulin receptor function to deblock insulin resistance and consequently enhance insulin sensitivity. As examples of the insulin sensitivity enhancer, the compound represented by the formula (I) or a pharmacologically acceptable salt thereof can be mentioned.

In the formula (I), as the hydrocarbon group in the optionally substituted hydrocarbon group represented by R, mention is made of aliphatic hydrocarbon groups, alicyclic hydrocarbon groups, alicyclic-aliphatic hydrocarbon groups, aromatic aliphatic hydrocarbon groups and aromatic hydrocarbon groups. Number of carbon atoms in these hydrocarbon groups is preferably 1 to 14.

The aliphatic hydrocarbon groups are preferably those having 1 to 8 carbon atoms. As the aliphatic hydrocarbon groups, mention is made of C_{1-8} saturated aliphatic hydrocarbon groups (e.g. alkyl group) as exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, hexyl, isohexyl, heptyl and octyl, and C_{2-8} unsaturated aliphatic hydrocarbon groups (e.g. alkenyl group, alkadienyl group, alkynyl group, alkadiynyl group) as exemplified by vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptynyl and 1-octynyl.

The alicyclic hydrocarbon groups are preferably those having 3 to 7 carbon atoms. As the alicyclic hydrocarbon groups, mention is made of C_{3-7} saturated alicyclic hydrocarbon groups (e.g. cycloalkyl group) as exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and C_{5-7} unsaturated alicyclic hydrocarbon groups (e.g. cycloalkenyl group, cycloalkadienyl group) as exemplified by 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl and 2,4-cycloheptadienyl.

As the alicyclic-aliphatic hydrocarbon groups, mention is made of, among those formed by combination of the above-mentioned alicyclic hydrocarbon groups with aliphatic hydrocarbon groups (e.g. cycloalkyl-alkyl group, cycloalkenyl-alkyl group), ones having 4 to 9 carbon atoms as exemplified by cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl and cycloheptylethyl.

The aromatic aliphatic hydrocarbon groups are preferably those having 7 to 13 carbon atoms (e.g. aralkyl group). As the aromatic aliphatic hydrocarbon groups, mention is made of C_{7-9} phenylalkyl as exemplified by benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and 1-phenylpropyl, and C_{11-13} naphthylalkyl as exemplified by α-naphthylmethyl, α-naphthylethyl, β-naphthylmethyl and β-naphthylethyl.

As the aromatic hydrocarbon groups, mention is made of, ones having 6 to 14 carbon atoms as exemplified by phenyl, naphthyl (α-naphtyl, β-naphthyl).

In the formula (I), as the heterocyclic group in the optionally substituted heterocyclic group represented by R, mention is made of, for example, 5- to 7-membered heterocyclic groups containing, as a ring component atom, 1 to 4 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom, and a condensed ring group. As the condensed ring, mention is made of, for example, these 5- to 7-membered heterocyclic groups condensed with 6-membered ring containing one or two nitrogen atoms, benzene ring or 5-membered ring containing one sulfur atom.

Examples of these heterocyclic groups include 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl,, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, 1H-indazol-3-yl, 1H-pyrrolo [2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 1H-imidazo[4,5-b]pyrazin-2-yl and benzopyranyl. Among them, pyridyl, oxazolyl or thiazolyl group is preferable.

In the formula (I), the hydrocarbon group and heterocyclic group represented by R may optionally have 1 to 5, preferably 1 to 3 substituents at any substitutable positions. Examples of such substituents include aliphatic hydrocarbon

group, alicyclic hydrocarbon group, aryl group, aromatic heterocyclic group, non-aromatic heterocyclic group, halogen atom, nitro group, optionally substituted amino group, optionally substituted acyl group, optionally substituted hydroxyl group, optionally substituted thiol group, optionally esterified carboxyl group, amidino group, carbamoyl group, sulfamoyl group, sulfo group, cyano group, azido group and nitroso group.

Examples of the aliphatic hydrocarbon groups include C_{1-15} straight-chain or branched aliphatic hydrocarbon groups as exemplified by alkyl group, alkenyl group, and alkynyl group.

Preferable examples of the alkyl group include C_{1-10} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, hexyl, pentyl, octyl, nonyl and decyl.

Preferable examples of the alkenyl group include C_{2-10} alkenyl groups such as vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl.

Preferable examples of the alkynyl group include C_{2-10} alkynyl groups such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As the alicyclic hydrocarbon group, mention is made of C_{3-12} saturated or unsaturated alicyclic hydrocarbon groups as exemplified by cycloalkyl group, cycloalkenyl group and cycloalkadienyl group.

Preferable examples of cycloalkyl group include C_{3-10} cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl and bicyclo[4.3.1]decyl.

Preferable examples of the cycloalkenyl group include C_{3-10} cycloalkenyl groups such as 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl and 3-cyclohexen-1-yl.

Preferable examples of the cycloalkadienyl group include C_{4-10} cycloalkadienyl groups such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl and 2,5-cyclohexadien-1-yl.

Preferable examples of the aryl group include C_{6-14} aryl groups such as phenyl, naphthyl (1-naphthyl, 2-naphthyl), anthryl, phenanthryl and acenaphthylenyl.

Preferable examples of the aromatic heterocyclic group include aromatic monocyclic heterocyclic groups such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl; and aromatic condensed heterocyclic groups such as benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, 1,2-benzoisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylidinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenathridinyl, phenathrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl.

Preferable examples of the non-aromatic heterocyclic group include oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidino, piperidino, morpholino and thiomorpholino.

Examples of the halogen atom include fluorine, chlorine, bromine and iodine.

As the substituted amino group in the optionally substituted amino group, mention is made of, N-monosubstituted amino group and N,N-disubstituted amino group. Examples of the substituted amino groups include amino groups having one or two substituents selected from C_{1-10} alkyl group, C_{2-10} alkenyl group, C_{2-10} alkynyl group, aromatic group, heterocyclic group and C_{1-10} acyl group (e.g. methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclohexylamino, phenylamino, N-methyl-N-phenyl-amino, acetylamino, propionylamino, benzoylamino and nicotinoylamino).

As the acyl group, mention is made of C_{1-13} acyl groups such as C_{1-10} alkanoyl group, C_{3-10} alkenoyl group, C_{4-10} cycloalkanoyl group, C_{4-10} cycloalkenoyl group and C_{6-12} aromatic carbonyl group.

Preferable examples of the C_{1-10} alkanoyl group include formyl acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl and octanoyl. Preferable examples of the C_{3-10} alkenoyl group include acryloyl, methacryloyl, crotonoyl and isocrotonoyl. Preferable examples of C_{4-10} cycloalkanoyl group include cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl and cycloheptanecarbonyl. Preferable examples of C_{4-10} cycloalkenoyl group include 2-cyclohexenecarbonyl. Preferable examples of C_{6-12} aromatic carbonyl group include benzoyl, naphthoyl and nicotinoyl.

As the substituent in the substituted acyl group, mention is made of, for example, C_{1-3} alkyl group, C_{1-3} alkoxy group, halogen atom (e.g. chlorine, fluorine, bromine, etc.), nitro group, hydroxyl group and amino group.

As the substituted hydroxyl group in the optionally substituted hydroxyl group, mention is made of, for example, alkoxy group, cycloalkyloxy group, alkenyloxy group, cycloalkenyloxy group, aralkyloxy group, acyloxy group and aryloxy group.

Preferable examples of the alkoxy group include C_{1-10} alkoxy groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, t.-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy and nonyloxy. Preferable examples of the cycloalkyloxy group include C_{3-10} cycloalkyloxy groups such as cyclobutoxy, cyclopentyloxy and cyclohexyloxy. Preferable examples of the alkenyloxy group include C_{2-10} alkenyloxy groups such as allyloxy, crotyloxy, 2-pentenyloxy and 3-hexenyloxy. Preferable examples of the cycloalkenyloxy group include C_{3-10} cycloalkenyloxy groups such as 2-cyclopentenyloxy and 2-cyclohexenyloxy. Preferable examples of the aralkyloxy group include C_{7-10} aryloxy groups such as phenyl-C_{1-4}alkyloxy (e.g. benzyloxy and phenethyloxy). Preferable examples of the acyloxy group include C_{2-13} acyloxy group, more preferably C_{2-4} alkanoy-

loxy groups (e.g. acetyloxy, propionyloxy, butyryloxy and isobutyryloxy). Preferable examples of the aryloxy group include C_{6-14} aryloxy groups such as phenoxy and naphthyloxy. The aryloxy group may optionally have one or two substituents such as halogen atom (e.g. chlorine, fluorine, bromine). Examples of the substituted aryloxy group include 4-chlorophenoxy.

As the substituted thiol group in the optionally substituted thiol group, mention is made of, alkylthio group, cycloalkylthio group, alkenylthio group, cycloalkenylthio group, aralkylthio group, acylthio group and arylthio group.

Preferable examples of the alkylthio group include C_{1-10} alkylthio groups such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec.-butylthio, t.-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio and nonylthio. Preferable examples of the cycloalkylthio group include C_{3-10} cycloalkylthio groups such as cyclobutylthio, cyclopentylthio and cyclohexylthio. Preferable examples of the alkenylthio group include C_{2-10} alkenylthio groups such as allylthio, crotylthio, 2-pentenylthio and 3-hexenylthio. Preferable examples of the cycloalkenylthio group include C_{3-10} cycloalkenylthio groups such as 2-cyclopentenylthio and 2-cyclohexenylthio. Preferable examples of the aralkylthio include C_{7-10} aralkylthio groups such as phenyl-C_{1-4}alkylthio (e.g. benzylthio and phenethylthio). Preferable examples of the acylthio group include C_{2-13} acylthio group, more preferably C_{2-4} alkanoylthio groups (e.g. acetylthio, propionylthio, butyrylthio and isobutyrylthio).

Preferable examples of the arylthio group include C_{6-14} arylthio groups such as phenylthio and naphthylthio. The arylthio group may optionally have one or two substituents such as halogen atom (e.g. chlorine, fluorine, bromine). Examples of the substituted arylthio group include 4-chlorophenylthio.

As the optionally esterified carboxyl group, mention is made of, for example, alkoxycarbonyl group, aralkyloxycarbonyl group and aryloxycarbonyl group.

Preferable examples of the alkoxycarbonyl group include C_{2-5} alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and butoxycarbonyl. Preferable examples of the aralkyloxycarbonyl group include C_{8-10} aralkyloxycarbonyl groups such as benzyloxycarbonyl. Preferable examples of the aryloxycarbonyl group include C_{7-15} aryloxycarbonyl groups such as phenoxycarbonyl and p-tolyloxycarbonyl.

Among the substituents on the hydrocarbon group and heterocyclic group represented by R, C_{1-10} alkyl groups, aromatic heterocyclic groups and C_{6-14} aryl groups are preferable, and C_{1-3} alkyl, furyl, thienyl, phenyl and naphthyl are especially preferable.

In the formula (I), substituents on the hydrocarbon group and heterocyclic group which are represented by R, may, when they are alicyclic hydrocarbon group, aryl group, aromatic heterocyclic group or non-aromatic heterocyclic group, have one or more, preferably 1 to 3, of suitable substituents respectively. Examples of these substituents include C_{1-6} alkyl groups, C_{2-6} alkenyl groups, C_{2-6} alkynyl groups, C_{3-7} cycloalkyl groups, C_{6-14} aryl groups, aromatic heterocyclic groups (e.g. thienyl, furyl, pyridyl, oxazolyl and thiazolyl), non-aromatic heterocyclic groups (e.g. tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolidino and piperazino), C_{7-9} aralkyl groups, amino group, N-mono-C_{1-4} alkylamino groups, N,N-di-C_{1-4} alkylamino groups, C_{2-8} acylamino groups (e.g. acetylamino, propionylamino and benzoylamino), amidino group, C_{2-8} acyl group (e.g. C_{2-8} alkanoyl groups), carbamoyl group, N-mono-C_{1-4} alkyl carbamoyl groups, N,N-di-C_{1-4} alkyl carbamoyl groups, sulfamoyl group, N-mono-C_{1-4} alkyl sulfamoyl groups, N,N-di-C_{1-4} alkyl sulfamoyl groups, carboxyl group, C_{2-8} alkoxycarbonyl groups, hydroxyl group, C_{1-4} alkoxy groups, C_{2-5} alkenyloxy groups, C_{3-7} cycloalkyloxy groups, C_{7-9} aralkyloxy groups, C_{6-14} aryloxy groups, mercapto group, C_{1-4} alkylthio groups, C_{7-9} aralkylthio groups C_{6-14} arylthio groups, sulfo group, cyano group, azido group, nitro group, nitroso group and halogen atom.

In the formula (I), R is preferably an optionally substituted heterocyclic group. R is more preferably pyridyl, oxazolyl or thiazolyl group which is optionally substituted by 1 to 3 substituents selected from C_{1-3} alkyl group, furyl group, thienyl group, phenyl group and naphthyl group.

R' in the formula (II) has the same definition as R except that R' does not represent benzopyranyl group when m and n are 0; X represents CH; A represents a bond; Q represents sulfur atom; R^1, L and M represent hydrogen atom; and ring E does not have further substituents.

In the formulae (I) and (II), Y represents —CO—, —CH(OH)— or —NR^3-. (wherein R^3 represents an optionally substituted alkyl group), preferably —CH(OH)— or —NR^3-. As the alkyl group in the optionally substituted alkyl group represented by R^3, mention is made of, for example, C_{1-4} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl and t.-butyl. Examples of the substituents include halogen (e.g., fluorine, chlorine, bromine and iodine), C_{1-4} alkoxy groups (e.g. methoxy, ethoxy, propoxy, butoxy, isobutoxy, sec.-butoxy and t.-butoxy), hydroxyl group, nitro group and C_{1-4} acyl groups (e.g. formyl, acetyl and propionyl).

The symbol m is 0 or 1, preferably 0.

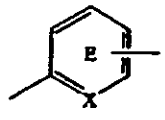
The symbol n is 0, 1 or 2, preferably 0 or 1.

X represents CH or N, preferably CH.

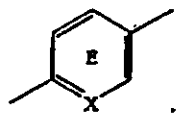
In the formulae (I) and (II), A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group. The aliphatic hydrocarbon group may be straight-chain or branched, and saturated or unsaturated. Specific examples of the aliphatic hydrocarbon group include saturated ones [e.g. —CH_2—, —$CH(CH_3)$—, —$(CH_2)_2$—, —$CH(C_2H_5)$—, —$(CH_2)_3$—, —$(CH_2)_4$—, —$(CH_2)_5$—, —$(CH_2)_6$— and —$(CH_2)_7$—] and unsaturated ones [e.g. —CH=CH—, —$C(CH_3)$=CH—, —CH=CH—CH_2—, —$C(C_2H_5)$=CH—, —CH_2—CH=CH—CH_2—, —CH_2—CH_2—CH=CH—CH_2—. —CH=CH—CH=CH—CH_2— and —CH=CH—CH=CH—CH=CH—CH_2—. A is preferably a bond or C_{1-4} divalent aliphatic hydrocarbon groups, the aliphatic hydrocarbon groups preferably being saturated. A is more preferably a bond or —$(CH_2)_2$—.

As the alkyl group represented by R^1, substantially the same one as the alkyl group in the above-mentioned R^3. R^1 is preferably hydrogen atom.

In the formulae (I) and (II), the partial formula:



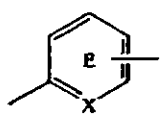
preferably represents the formula:



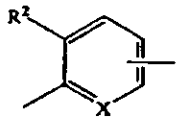
Ring E has 1 to 4 substituents at any substitutable positions. Examples of such substituents include alkyl group, optionally substituted hydroxyl group, halogen atom, optionally substituted acyl group and optionally substituted amino group. These substituents have substantially the same

meaning as those described as substituents of the hydrocarbon group and heterocyclic group represented by R.

Ring E, namely the partial formula:



preferably represents the formula:



wherein R^2 represents hydrogen atom, an alkyl group, an optionally substituted hydroxyl group, a halogen atom, an optionally substituted acyl group, nitro group or an optionally substituted amino group.

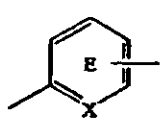
As the alkyl group, optionally substituted hydroxyl group, halogen atom, optionally substituted acyl group and optionally substituted amino group represented by R^2, mention is made of those described as substituents of the hydrocarbon group and heterocyclic group represented by R. R^2 is preferably hydrogen atom, optionally substituted hydroxyl group or halogen atom, more preferably hydrogen atom or optionally substituted hydroxyl group, especially preferably hydrogen atom or C_{1-4} alkoxy groups.

In the formulae (I) and (II), L and M represent hydrogen atom, or they may optionally be combined with each other to form a bond. L and M are preferably hydrogen atom.

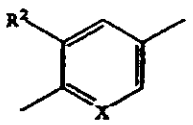
In the compounds wherein L and M are combined with each other to form a bond, there exist (E)- and (Z)-isomers relative to the double bond at the 5-position of the azolidinedione ring.

And, in the compounds wherein L and M respectively represent hydrogen atom, there exist (R)- and (S)-optical isomers due to the asymmetric carbon at the 5-position of the azolidinedione ring. The compounds include these (R)- and (S)-optical isomers and racemic isomers.

Preferable examples of the compounds represented by the formula (I) or (II) includes those in which R is pyridyl, oxazolyl or thiazolyl group optionally having 1 to 3 substituents selected from C_{1-3} alkyl, furyl, thienyl, phenyl and naphthyl; m is 0; n is 0 or 1; X is CH; A is a bond or $-(CH_2)_2-$; R^1 is hydrogen atom; ring E, namely the partial formula:



represents the formula:



and R^2 is hydrogen atom or C_{1-4} alkoxy group; and L and M are both hydrogen atom.

Preferable examples of the compound represented by the formula (I) include

(1) the compound represented by the formula (III) such as 5-[4-[2-(3-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione; 5-[4-[2-(4-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione; 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (generic name: pioglitazone); and 5-[4-[2-(6-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione;

(2) (R)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione; and

(3) 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (generic name: troglitazone/CS-045).

The compound represented by the formula (I) is especially preferably pioglitazone.

The compound represented by the formula (II) is preferably the compound represented by the formula (III) and (R)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione, more preferably pioglitazone.

The pharmacologically acceptable salt of the compound represented by the formula (I) or (II) are exemplified by salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

Preferable examples of salts with inorganic bases include salts with alkali metals such as sodium, potassium, etc., salts with alkaline earth metals such as calcium, magnesium, etc., and salts with aluminum, ammonium, etc.

Preferable examples of salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, etc.

Preferable examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.

Preferable examples of salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid., benzenesulfonic acid, p-toluenesulfonic acid, etc.

Preferable examples of salts with basic amino acids include salts with arginine, lysine, ornithine, etc., and preferable examples of salts with acidic amino acids include salts with aspartic acid, glutamic acid, etc.

The pharmacologically acceptable salt of the compound represented by the formula (III) is preferably a salt with an inorganic acid, more preferably a salt with hydrochloric acid. Especially, pioglitazone is preferably used in the form of salt with hydrochloric acid.

The compounds represented by the formula (I) or (II) or a salt thereof can be produced in accordance with, for example, methods described in JPA S55(1980)-22636(EP-A 8203), JPA S60(1985)-208980(EP-A 155845), JPA S61(1986)-286376(EP-A 208420), JPA S61(1986)-85372(EP-A 177353), JPA S61(1986)-267580(EP-A 193256), JPA H5(1993)-86057(WO 92/18501), JPA H7(1995)-82269 (EP-A 605228), JPA H7(1995)-101945(EP-A 612743), EP-A 643050, EP-A 710659, etc. or methods analogous thereto.

Insulin sensitivity enhancers include 5-[[3,4-dihydro-2-(phenylmethyl)-2H-1-benzopyran-6-yl]methyl]-2,4-thiazolidinedione (generic name: englitazone) or its sodium salt;

5-[[4-[3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl]phenyl]methyl]-2,4-thiazolidinedione (generic name: darglitazone/CP-86325) or its sodium salt;

5-[2-(5-methyl-2-phenyl-4-oxazolylmethyl)benzofuran-5-ylmethyl]-2,4-oxazolidinedione (CP-92768);

5-(2-naphthalenylsulfonyl)-2,4-thiazolidinedione (AY-31637);

4-[(2-naphthalenyl)methyl]-3H-1,2,3,5-oxathiadiazol-2-oxide (AY-30711); and

5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]-methyl]-2,4-thiazolidinedione (BRL-49653), etc. in addition to compounds mentioned hereinbefore.

In the present invention, examples of the drug which is used in combination with the above-mentioned insulin sensitivity enhancer include an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor.

α-Glucosidase inhibitors are drugs which inhibit digestive enzymes such as amylase, maltase, α-dextrinase, sucrase, etc. to retard digestion of starch and sugars. Examples of the α-glucosidase inhibitors include acarbose, N-(1,3-dihydroxy-2-propyl)valiolamine (generic name; voglibose), miglitol, etc. with preferance given to voglibose.

Aldose reductase inhibitors are drugs which inhibit the first-stage rate-limitting enzyme in the polyol pathway to prevent or arrest diabetic complications. In the hyperglycemic state of diabetes, the utilization of glucose in the polyol pathway is increased and the excess sorbitol accumulated intracellularly as a consequence acts as a tissue toxin and hence evokes the onset of complications such as diabetic neuropathy, retinopathy, and nephropathy. Examples of the aldose reductase inhibitors include tolurestat; epalrestat; 3,4-dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxazine-4-acetic acid; 2,7-difluorospiro(9H-fluorene-9,4'-imidazolidine)-2',5'-dione (generic name: imirestat);

3-[(4-bromo-2-fluorophenyl)methyl]-7-chloro-3,4-dihydro-2,4-dioxo-1(2H)-quinazoline acetic acid (generic name: zenarestal);

6-fluoro-2,3-dihydro-2',5'-dioxo-spiro(4H-1-benzopyran-4,4'-imidazolidine]-2-carboxamide (SNK-860); zopolrestat; sorbinil; and

1-[(3-bromo-2-benzofuranyl)sulfonyl]-2,4-imidazolidinedione (M-16209), etc.

Biguanides are drugs having actions of stimulation of anaerobic glycolysis, increase of the sensitivity to insulin in the peripheral tissues, inhibition of glucose absorption from the intestine, suppression of hepatic gluconeogenesis, and inhibition of fatty acid oxidation. Examples of the biguanides include phenformin, metformin, buformin etc.

Statin compounds are drugs having actions of lowering blood cholesterol levels by inhibiting hydroxymethylglutalyl CoA (HMG-CoA) reductase. Examples of the statin compounds include pravastatin and its sodium salt, simvastatin, lovastatin, atorvastatin, fluvastatin, etc.

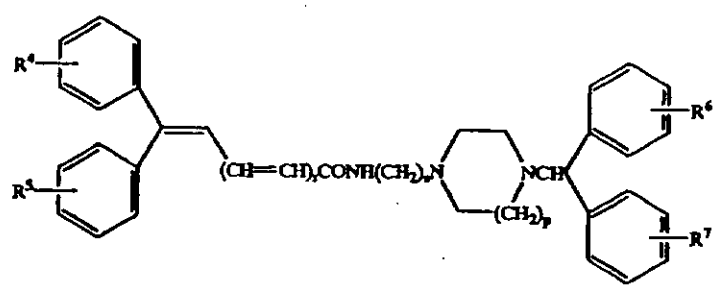
Squalene synthesis inhibitors are drugs having actions of lowering blood cholesterol levels by inhibiting synthesis of squalene. Examples of the squalene synthesis inhibitors include (S)-α-[Bis[2,2-dimethyl-1-oxopropoxy)methoxy] phosphinyl]-3-phenoxybenzenebutanesulfonic acid, mono potassium salt (BMS-188494).

Fibrate compounds are drugs having actions of lowering blood cholesterol levels by inhibiting synthesis and secretion of triglycerides in liver and activating a lipoprotein lipase.

Examples of the fibrate compounds include bezafibrate, beclobrate, binifibrate, ciplofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate, etc.

LDL catabolism enhancers are drugs having actions of lowering blood cholesterol levels by increasing the number of LDL (low-density lipoprotein) receptors.

Examples of the LDL catabolism enhancers include the compound which is described in JPA H7(1995)-316144 and represented by the formula:



wherein R^4, R^5, R^6 and R^7 are the same or different, and represent hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group; r is 0–2; s is 2–4; p is 1–2; or a salt thereof; specifically N-[2-[4-bis(4-fluorophenyl) methyl-1-piperazinyl]ethyl]-7,7-diphenyl-2,4,6-heptatrienic acid amide, etc.

The above-mentioned statin compounds, squalene synthesis inhibitors, fibrate compounds and LDL catabolism enhancers can be substituted with other drugs having the property to lower blood cholesterol and triglyceride levels. Examples of these drugs include nicotinic acid derivatives such as nicomol and niceritrol; antioxidants such as probucol; and ion-exchange resins such as colestyramin.

Angiotensin converting enzyme inhibitors are drugs having actions of partially lowering blood glucose levels as well as lowering blood pressure by inhibiting angiotensin converting enzymes. Examples of the angiotensin converting enzyme inhibitors include captopril, enalapril, alacepril, delapril, ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moveltopril, perindopril, quinapril, spirapril, temocapril, trandolapril, etc.

In the present invention, especially preferred is the pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with an α-glucosidase inhibitor. The insulin sensitivity enhancer is especially preferably pioglitazone, and the α-glucosidase inhibitor is especially preferably voglibose.

In the present invention, examples of the drug which is used in combination with the compound represented by the formula (II) or a pharmacologically acceptable salt thereof include an insulin secretion enhancer and/or an insulin preparation.

Insulin secretion enhancers are drugs having the property to promote secretion of insulin from pancreatic β cells. Examples of the insulin secretion enhancers include sulfonylureas (SU). The sulfonylureas (SU) are drugs which promote secretion of insulin from pancreatic β cells by transmitting signals of insulin secretion via SU receptors in the cell membranes. Examples of the SU include tolbutamide; chlorpropamide; tolazamide; acetohexamide; 4-chloro-N-[(1-pyrolidinylamino)carbonyl]-benzenesulfonamide (generic name: glycopyramide) or its ammonium salt; glibenclamide (glyburide); gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; tolcyclamide, etc.

Insulin secretion enhancers include N-[[4-(1-methylethyl) cyclohexyl]carbonyl]-D-phenylalanine (AY-4166); calcium

(2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl) propionate dihydrate (KAD-1229); and glimepiride (Hoe 490), etc. in addition to compounds mentioned hereinbefore. The insulin secretion enhancer is especially preferably glibenclamide.

Examples of the insulin preparations include animal insulin preparations typically extracted from bovine or porcine pancreas and human insulin preparations synthesized by genetic engineering techniques typically using *Escherichia coli* or yeasts. While insulin preparations are available in a variety of types, e.g. immediate-acting, bimodal-acting, intermediate-acting, and long-acting, these types of preparations can be selectively administered according to the patient's condition.

In the present invention, especially preferred is the pharmaceutical composition which comprises the compound represented by the formula (II) or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer. The compound represented by the formula (II) or a pharmacologically acceptable salt thereof is especially preferably pioglitazone, and the insulin secretion enhancer is especially preferably glibenclamide.

The pharmaceutical composition comprising an insulin sensitivity enhancer in combination with at least one member selected from the group consisting of an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor; and the pharmaceutical composition comprising the compound represented by the formula (II) or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation, both provided in accordance with the present invention, can be respectively put to use by mixing the respective active components either all together or independently with a physiologically acceptable carrier, excipient, binder, diluent, etc. and administering the mixture or mixtures either orally or non-orally as a pharmaceutical composition. When the active components are formulated independently, the respective formulations can be extemporaneously admixed using a diluent or the like and administered or can be administered independently of each other, either concurrently or at staggered times to the same subject.

The dosage form for said pharmaceutical composition includes such oral dosage forms as granules, powders, tablets, capsules, syrups, emulsions, suspensions, etc. and such non-oral dosage forms as injections (e.g. subcutaneous, intravenous, intramuscular and intraperitoneal injections), drip infusions, external application forms (e.g. nasal spray preparations, transdermal preparations, ointments, etc.), and suppositories (e.g. rectal and vaginal suppositories).

These dosage forms can be manufactured by the per se known technique conventionally used in pharmaceutical procedures. The specific manufacturing procedures are as follows.

To manufacture an oral dosage form, an excipient (e.g. lactose, sucrose, starch, mannitol, etc.), a disintegrator (e.g. calcium carbonate, carboxymethylcellulose calcium, etc.), a binder (e.g. α-starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, etc.), and a lubricant (e.g. talc, magnesium stearate, polyethylene glycol 6000, etc.), for instance, are added to the active component or components and the resulting composition is compressed. Where necessary, the compressed product is coated, by the per se known technique, for masking the taste or for enteric dissolution or sustained release. The coating material that can be used includes, for instance, ethylcellulose, hydroxymethylcellulose, polyoxyethylene glycol, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, and Eudragit (Rohm & Haas, Germany, methacrylic-acrylic copolymer).

Injections can be manufactured typically by the following procedure. The active component or components are dissolved, suspended or emulsified in an aqueous vehicle (e.g. distilled water, physiological saline, Ringer's solution, etc.) or an oily vehicle (e.g. vegetable oil such as olive oil, sesame oil, cottonseed oil, corn oil, etc. or propylene glycol) together with a dispersant (e.g. Tween 80 (Atlas Powder, U.S.A.), HCO 60 (Nikko Chemicals), polyethylene glycol, carboxymethylcellulose, sodium alginate, etc.), a preservative (e.g. methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, benzyl alcohol, chlorobutanol, phenol, etc.), an isotonizing agent (e.g. sodium chloride, glycerol, sorbitol, glucose, inverted sugar, etc.) and other additives. If desired, a solubilizer (e.g. sodium salicylate, sodium acetate, etc.), a stabilizer (e.g. human serum albumin), a soothing agent (e.g. benzalkonium chloride, procaine hydrochloride, etc.) and other additives can also be added.

A dosage form for external application can be manufactured by processing the active component or components into a solid, semi-solid or liquid composition. To manufacture a solid composition, for instance, the active component or components, either as they are or in admixture with an excipient (e.g. lactose, mannitol, starch, microcrystalline cellulose, sucrose, etc.), a thickener (e.g. natural gums, cellulose derivatives, acrylic polymers, etc.), etc., are processed into powders. The liquid composition can be manufactured in substantially the same manner as the injections mentioned above. The semi-solid composition is preferably provided in a hydrous or oily gel form or an ointment form. These compositions may optionally contain a pH control agent (e.g. carbonic acid, phosphoric acid, citric acid, hydrochloric acid, sodium hydroxide, etc.), and a preservative (e.g. p-hydroxybenzoic acid esters, chlorobutanol, benzalkonium chloride, etc.), among other additives.

Suppositories can be manufactured by processing the active component or components into an oily or aqueous composition, whether solid, semi-solid or liquid. The oleaginous base that can be used includes, for instance, higher fatty acid glycerides [e.g. cacao butter, Witepsols (Dinamit-Nobel), etc.], medium-chain fatty acids [e.g. Migriols (Dinamit-Nobel), etc.], vegetable oils (e.g. sesame oil, soybean oil, cotton-seed oil, etc.), etc. The water-soluble base includes, for instance, polyethylene glycols, propylene glycol, etc. The hydrophilic base includes, for instance, natural gums, cellulose derivatives, vinyl polymers, and acrylic polymers, etc.

The pharmaceutical composition of the present invention is low in toxicity and can be safely used in mammals (e.g. humans, mice, rats, rabbits, dogs, cats, bovines, horses, swines, monkeys).

The dosage of the pharmaceutical composition of the present invention may be appropriately determined with reference to the dosages recommended for the respective active components and can be selected appropriately according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of the active components, among other factors. For example, the dosage of the insulin sensitivity enhancer for an adult can be selected from the clinical oral dose range of 0.01 to 10 mg/kg body weight (preferably 0.05 to 10 mg/kg body weight, more preferably 0.05 to 5 mg/kg body weight) or the clinical parenteral dose range of 0.005 to 10 mg/kg body

weight (preferably 0.01 to 10 mg/kg body weight, more preferably 0.01 to 1 mg/kg body weight). The other active component or components having different modes of action for use in combination can also be used in dose ranges selected by referring to the respective recommended clinical dose ranges. The preferred frequency of administration is 1 to 3 times a day.

The proportions of the active components in the pharmaceutical composition of the present invention can be appropriately selected according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of active components, among other factors. When, for example, the compound represented by the formula (I) or a pharmacologically acceptable salt thereof (e.g. pioglitazone) which is the insulin sensitivity enhancer and voglibose which is an α-glucosidase inhibitor are to be administered in combination to a human subject, voglibose is used in a proportion of usually about 0.0001 to 0.2 weight parts and preferably about 0.001 to 0.02 weight parts relative to 1 weight part of the compound or a salt thereof. When, for example, the compound represented by the formula (II) or a pharmacologically acceptable salt thereof and glibenclamide which is an insulin secretion enhancer are to be administered in combination to a human subject, glibenclamide is used in a proportion of usually about 0.002 to 5 weight parts and preferably about 0.025 to 0.5 weight parts, relative to 1 weight part of the compound or a pharmacologically acceptable salt thereof.

The pharmaceutical composition of the present invention shows a marked synergistic effect compared with administration of either active component alone. For example, compared with cases in which each of these active components was administered to diabetic Wistar fatty rats with genetical obsesity, administration of these active components in combination resulted in marked improvements in both hyperglycemia and reduced glucose tolerance. Thus, the pharmaceutical composition of the present invention lowers blood glucose in diabetics more effectively than it is the case with administration of each component drug alone and, therefore, can be used advantageously for the prophylaxis and treatment of diabetic complications.

Furthermore, since the pharmaceutical composition of the present invention develops sufficient efficacy with reduced doses as compared with the administration of any one of the active components alone, the side effects of the respective components (e.g. gastrointestinal disorders such as diarrhea, etc.) can be reduced.

The following working examples and experimental examples are merely intended to illustrate the present invention in further detail but should by no means be construed as defining the scope of the invention.

The pharmaceutical composition of the present invention can be prepared according to the following formulations.

WORKING EXAMPLE 1

Capsules

(1) Pioglitazone hydrochloride	30 mg
(2) Voglibose	0.2 mg
(3) Lactose	60 mg
(4) Microcrystalline cellulose	79.8 mg
(5) Magnesium stearate	10 mg
Total	180 mg

The whole amounts of (1), (2), (3) and (4) and half the amount of (5) are mixed well and granulated in the conventional manner. Then, the balance of (5) is added and, after mixing, the whole composition is filled in a gelatin hard capsule shell.

WORKING EXAMPLE 2

Tablets

(1) Pioglitazone hydrochloride	10 mg
(2) Glibenclamide	1.25 mg
(3) Lactose	86.25 mg
(4) Corn starch	20 mg
(5) Polyethylene glycol	2.5 mg
(6) Hydroxypropylcellulose	4 mg
(7) Carmellose calcium	5.5 mg
(8) Magnesium stearate	0.5 mg
	130 mg (per tablet)

The whole amounts of (1), (2), (3), (4), and (5), ⅗ amounts of (6) and (7), and ½ amount of (8) are mixed well and granulated in the conventional manner. Then, the balances of (6), (7) and (8) are added to the granules, which is mixed well and the whole composition is compressed with a tablet machine. The adult dosage is 3 tablets/day, to be taken in 1 to 3 divided doses.

WORKING EXAMPLE 3

Capsules

(1) Pioglitazone hydrochloride	10 mg
(2) Epalrestat	50 mg
(3) Lactose	55 mg
(4) Microcrystalline cellulose	55 mg
(5) Magnesium stearate	10 mg
Total	180 mg

The whole amounts of (1), (2), (3) and (4) and ½ amount of (5) are mixed well and granulated in the conventional manner. Then, the balance of (5) is added and the whole composition is filled in gelatin capsule shell. The adult dosage is 3 capsules/day, to be taken in 1 to 3 divided doses.

EXPERIMENTAL EXAMPLE 1

Effect of pioglitazone hydrochloride in combination with α-glucosidase inhibitor in genetically obese and diabetic Wistar fatty rats

Male Wistar fatty rats aged 14–19 weeks were divided into 4 groups of 5–6, and pioglitazone hydrochloride (1 mg/kg body wt./day, p.o.) and/or voglibose (an α-glucosidase inhibitor) (0.31 mg/kg body wt./day; administered by mixing in commercial diet at a rate of 5 ppm) was administered for 14 days. The blood was then collected from

the tail vein and the plasma glucose and hemoglobin A_1 were determined by the enzymatic method (Encore Chemical System, Baker) and using a commercial kit (NC-ROPET, Nippon Chemiphar Co.), respectively. The results were expressed in mean±standard deviation for each group (n=5–6) and analyzed by Dunnett's test, which are shown in Table 1. The 1% level of significance was used.

TABLE 1

Group	Plasma glucose (mg/dl)	Hemoglobin A_1 (%)
Control	345 ± 29	5.7 ± 0.4
Pioglitazone	215 ± 50*	5.2 ± 0.3
Voglibose	326 ± 46	6.0 ± 0.6
Pioglitazone + voglibose	114 ± 23*	4.5 ± 0.4*

*: P < 0.01 vs. control group

It is apparent from Table 1 that both the blood glucose and hemoglobin A_1 levels were remarkably lowered by combined administration of pioglitazone and voglibose as compared with the administration of either drug alone.

EXPERIMENTAL EXAMPLE 2

Effect of pioglitazone hydrochloride in combination with an insulin secretion enhancer in genetically obese and diabetic Wistar fatty rats

Male Wistar fatty rats aged 13–14 weeks were divided into 4 groups of 5, and pioglitazone hydrochloride (3 mg/kg/day, p.o.) and/or glibenclamide (an insulin secretion enhancer) (3 mg/kg/day, p.o.) was administered for 7 days. Following an overnight fast, the oral glucose loading test (2 g glucose/kg/5 ml, p.o.) was carried out. Prior to glucose loading and 120 and 240 minutes after the loading, blood was collected from the tail vein and the plasma glucose was assayed by the enzymatic method (Encore Chemical System, Baker). The results were expressed in mean±SD for each group (n=5) and analyzed by Dunnett's test, which are shown in Table 2.

TABLE 2

Group	Plasma glucose (mg/dl) 0 min.	120 min.	240 min.
Control	119 ± 9	241 ± 58	137 ± 10
Pioglitazone	102 ± 12	136 ± 17*	102 ± 9*
Glibenclamide	118 ± 12	222 ± 61	106 ± 24*
Pioglitazone + glibenclamide	108 ± 3	86 ± 10*	60 ± 5*

*: P < 0.01 vs. control group

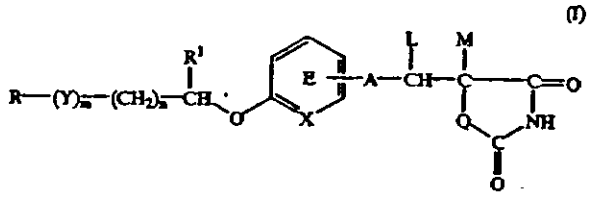
It is apparent from Table 2 that the increase of blood sugar following glucose loading was remarkably inhibited by the combined administration of pioglitazone and glibenclamide as compared with the administration of either drug alone.

The pharmaceutical composition of the present invention shows a potent depressive effect on diabetic hyperglycemia and is useful for prophylaxis and treatment of diabetes. Moreover, this pharmaceutical composition is useful for prophylaxis and treatment of diabetic complications such as diabetic neuropathy, nephropathy, retinopathy, macroangiopathy, and osteopenia. In addition, by appropriately selecting the kinds of component drugs, administration route, dosage, etc. according to clinical status, stable hypoglycemic efficacy in long-term therapy can be expected with an extremely low risk of side effect.

What is claimed is:

1. A method for reducing the amount of active components administered to a diabetic patient, which comprises administering to said patient a therapeutically effective amount of an insulin sensitivity enhancer in combination with a biguanide as said active components.

2. The method according to claim 1, wherein the insulin sensitivity enhancer is a compound represented by the formula:



(I)

wherein R represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR^3- wherein R^3 represents an optionally substituted alkyl group; m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R^1 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 further substituents, and the substituents may optionally be combined with R^3 to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; or a pharmacologically acceptable salt thereof.

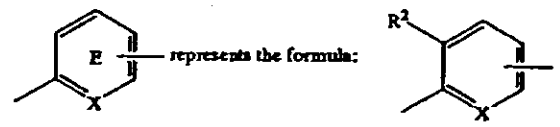
3. The method according to claim 2, wherein R is an optionally substituted heterocyclic group.

4. The method according to claim 2, wherein m is 0.

5. The method according to claim 2, wherein X is CH.

6. The method according to claim 2, wherein R^1 is hydrogen atom.

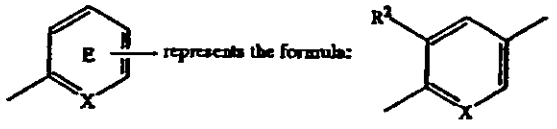
7. The method according to claim 2, wherein the partial formula:



wherein R^2 represents hydrogen atom, an alkyl group, an optionally substituted hydroxyl group, a halogen atom, an optionally substituted acyl group, nitro group or an optionally substituted amino group.

8. The method according to claim 2, wherein L and M are hydrogen atoms.

9. The method according to claim 2, wherein R is pyridyl, oxazolyl or thiazolyl group optionally having 1 to 3 substituents selected from C_{1-3} alkyl, furyl, thienyl, phenyl and naphthyl; m is 0; n is 0 or 1; X is CH; A is a bond or $—(CH_2)_2—$; R^1 is hydrogen atom; wherein the partial formula:



and wherein R^2 is hydrogen atom or C_{1-4} alkoxy group; and L and M are both hydrogen atoms.

10. The method according to claim 2, wherein the compound represented by the formula (I) is pioglitazone or its hydrochloride.

11. The method according to claim 1, wherein the biguanide is selected from the group consisting of phenformin, metformin and buformin.

12. The method according to claim 1, wherein the biguanide is metformin.

13. The method according to claim 1, wherein the insulin sensitivity enhancer is pioglitazone or its hydrochloride and the biguanide is metformin.

14. The method according to claim 1, wherein the insulin sensitivity enhancer is troglitazone.

15. The method according to claim 1, wherein the insulin sensitivity enhancer is 5-[[4-[2-(methyl-2-pyridylamino) ethoxy]phenyl]-methyl]-2,4-thiazolidinedione or its pharmacologically acceptable salt.

16. The method according to claim 1, wherein the insulin sensitivity enhancer and biguanide are mixed together to form an admixture and the admixture is administered to the mammal.

17. The method according to claim 1, wherein the insulin sensitivity enhancer and biguanide are not mixed together but are administered independently to the mammal.

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US006172090B1

(12) **United States Patent**
Ikeda et al.

(10) **Patent No.: US 6,172,090 B1**
(45) **Date of Patent: Jan. 9, 2001**

(54) **PHARMACEUTICAL COMPOSITION**

(75) Inventors: **Hitoshi Ikeda, Higashiosaka; Takashi Sohda, Takatsuki; Hiroyuki Odaka, Kobe, all of (JP)**

(73) Assignee: **Takeda Chemical Industries, Ltd., Osaka (JP)**

(*) Notice: Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

(21) Appl. No.: **09/303,495**

(22) Filed: **Apr. 30, 1999**

Related U.S. Application Data

(62) Division of application No. 09/057,465, filed on Apr. 9, 1998, now Pat. No. 5,965,584, which is a division of application No. 08/667,979, filed on Jun. 19, 1996, now Pat. No. 5,952,356.

(30) **Foreign Application Priority Data**

Jun. 20, 1995 (JP) 7-153500

(51) Int. Cl.[7] A61K 31/44; A61K 31/425; A61K 31/42; A61K 31/155

(52) U.S. Cl. 514/342; 514/369; 514/376; 514/635; 514/866

(58) Field of Search 514/342, 369, 514/376, 635, 866

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(57) **ABSTRACT**

Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with other antidiabetics differing from the enhancer in the mechanism of action, which shows a potent depressive effect on diabetic hyperglycemia and is useful for prophylaxis and treatment of diabetes.

17 Claims, No Drawings

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PHARMACEUTICAL COMPOSITION

This is a divisional application of Ser. No. 09/057,465, filed Apr. 9, 1998, U.S. Pat. No. 5,965,584 which was a divisional application of Ser. No. 08/667,979, filed Jun. 19, 1996 now U.S. Pat. No. 5,956,356.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a pharmaceutical composition comprising an insulin sensitivity enhancer in combination with one or more other antidiabetics differing from said enhancer in the mechanism of action.

2. Description of Related Art

Recent years, the pathology of diabetes has become more and more understood and, in parallel, drugs specific for the respective pathologic states have been developed. Accordingly a variety of drugs having new mechanism of action have appeared one after another.

Insulin sensitivity enhancers are also known as insulin resistance deblockers because they have the action to normalize the impaired insulin receptor function, and are gathering much attention in these years.

Regarding such insulin sensitivity enhancers, a very useful compound such as pioglitazone has been developed [Fujita et al., Diabetes 32, 804–810, 1983, JP-A S55(1980)-22636 (EP-A 8203), JP-A S61(1986)-267580 (EP-A 193256)]. Pioglitazone restores the impaired insulin receptor function to normalize the uneven distribution of glucose transporters in cells, the cardinal enzyme systems associated with glycometabolism, such as glucokinase, and enzyme systems associated with lipidmetabolism, such as lipoprotein lipase. As the results, insulin resistance are deblocked to improve glucose tolerance, and lower the plasma concentrations of neutral lipids and free fatty acids. Since these actions of pioglitazone are comparatively gradual and the risk of side effect in long-term administration is also low, this compound is useful for obese patients who are presumed to be highly insulin-resistant.

Also, insulin sensitivity enhancers such as CS-045, thazolidinedione derivatives and substituted thiazolidinedione derivatives are reported to be used in combination with insulin [JP-A H4(1992)-66579, JP-A H4(1992)-69383, JP-A H5(1993)-202042]. However, the pharmaceutical composition having a specific combination of the present invention is unknown.

Diabetes is a chronic disease with diverse pathologic manifestations and is accompanied by lipidmetabolism disorders and circulatory disorders as well as glycometabolism disorders. As the results, diabetes tends to progress entailing various complications in many cases. Therefore, it is necessary to select the drug of choice for the prevailing disease state in each individual case. However, this selection is often difficult in clinical settings because single use of each individual drug can not bring sufficient effects in some disease states and there are various problems such as side effect which is caused by an increased dose or a long-term administration.

SUMMARY OF THE INVENTION

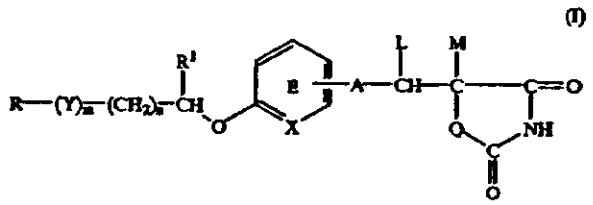
In view of the above state of the art, the inventors of the present invention did much research to develop antidiabetics which would not virtually cause adverse reactions even on long-term administration and could be effective for a large cohort of the diabetic population. As a consequence, they

discovered that the above object can be accomplished by using an insulin sensitivity enhancer, such as the drug described above, in combination with other antidiabetics differing from said enhancer in the mechanism of action, and accordingly have perfected the present invention.

The present invention, therefore, relates to:

1) Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with at least one member of the group consisting of an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor;

2) Pharmaceutical composition according to 1), wherein the insulin sensitivity enhancer is a compound represented by the formula:



(I)

wherein R represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR^3— (wherein R^3 represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R^1 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 substituents, and the substituents may optionally be combined with R^1 to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; or a pharmacologically acceptable salt thereof;

3) Pharmaceutical composition according to 2), wherein the compound represented by the formula (I) is pioglitazone;

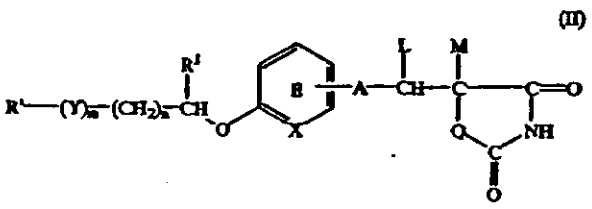
4) Pharmaceutical composition according to 1), which comprises an insulin sensitivity enhancer in combination with an α-glucosidase inhibitor;

5) Pharmaceutical composition according to 4), wherein the α-glucosidase inhibitor is voglibose;

6) Pharmaceutical composition according to 4), wherein the insulin sensitivity enhancer is pioglitazone and the α-glucosidase inhibitor is voglibose;

7) Pharmaceutical composition according to 1), which is for prophylaxis or treatment of diabetes;

8) Pharmaceutical composition which comprises a compound represented by the formula:



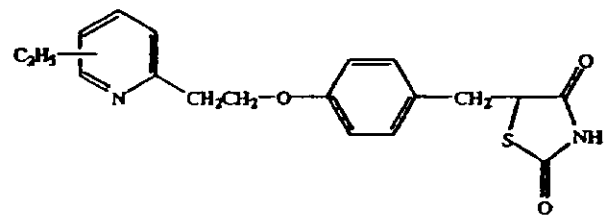
(II)

wherein R' represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group

represented by —CO—, —CH(OH)— or —NR³— (wherein R³ represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R¹ represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 substituents, and the substituents may optionally be combined with R¹ to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; with a proviso that R' does not represent benzopyranyl group when m and n are O, X represents CH, A represents a bond, Q represents sulfur atom, R¹, L and M represent hydrogen atom and ring E does not have further substituents; or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation;

9) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is the compound represented by the formula:

(III)



10) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is pioglitazone;

11) Pharmaceutical composition according to 8), wherein the insulin secretion enhancer is glibenclamide;

12) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is pioglitazone and the insulin secretion enhancer is glibenclamide;

13) Pharmaceutical composition according to 8), which is for prophylaxis or treatment of diabetes.

DETAILED DESCRIPTION OF THE INVENTION

The term "insulin sensitivity enhancer" as used in this specification means any and all drug substances that restore the impaired insulin receptor function to deblock insulin resistance and consequently enhance insulin sensitivity. As examples of the insulin sensitivity enhancer, the compound represented by the formula (I) or a pharmacologically acceptable salt thereof can be mentioned.

In the formula (I), as the hydrocarbon group in the optionally substituted hydrocarbon group represented by R, mention is made of aliphatic hydrocarbon groups, alicyclic hydrocarbon groups, alicyclic-aliphatic hydrocarbon groups, aromatic aliphatic hydrocarbon groups and aromatic hydrocarbon groups. Number of carbon atoms in these hydrocarbon groups is preferably 1 to 14.

The aliphatic hydrocarbon groups are preferably those having 1 to 8 carbon atoms. As the aliphatic hydrocarbon groups, mention is made of C_{1-8} saturated aliphatic hydrocarbon groups (e.g. alkyl group) as exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, hexyl, isohexyl, heptyl and octyl, and C_{2-8} unsaturated aliphatic hydrocarbon groups (e.g. alkenyl group, alkadienyl group, alkynyl group, alkadiynyl group) as exemplified by vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl; 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl; 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptynyl and 1-octynyl.

The alicyclic hydrocarbon groups are preferably those having 3 to 7 carbon atoms. As the alicyclic hydrocarbon groups, mention is made of C_{3-7} saturated alicyclic hydrocarbon groups (e.g. cycloalkyl group) as exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and C_{5-7} unsaturated alicyclic hydrocarbon groups (e.g. cycloalkenyl group, cycloalkadienyl group) as exemplified by 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl and 2,4-cycloheptadienyl.

As the alicyclic-aliphatic hydrocarbon groups, mention is made of, among those formed by combination of the above-mentioned alicyclic hydrocarbon groups with aliphatic hydrocarbon groups (e.g. cycloalkyl-alkyl group, cycloalkenyl-alkyl group), ones having 4 to 9 carbon atoms as exemplified by cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl and cycloheptylethyl.

The aromatic aliphatic hydrocarbon groups are preferably those having 7 to 13 carbon atoms (e.g. aralkyl group). As the aromatic aliphatic hydrocarbon groups, mention is made of C_{7-9} phenylalkyl as exemplified by benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and 1-phenylpropyl, and C_{11-13} naphthylalkyl as exemplified by α-naphthylmethyl, α-naphthylethyl, β-naphthylmethyl and β-naphthylethyl.

As the aromatic hydrocarbon groups, mention is made of, ones having 6 to 14 carbon atoms as exemplified by phenyl, naphthyl (α-naphtyl, β-naphthyl).

In the formula (I), as the heterocyclic group in the optionally substituted heterocyclic group represented by R, mention is made of, for example, 5- to 7-membered heterocyclic groups containing, as a ring component atom, 1 to 4 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom, and a condensed ring group. As the condensed ring, mention is made of, for example, these 5- to 7-membered heterocyclic groups condensed with 6-membered ring containing one or two nitrogen atoms, benzene ring or 5-membered ring containing one sulfur atom.

Examples of these heterocyclic groups include 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, 1H-indazol-3-yl, 1H-pyrrolo [2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-

2-yl, 1H-imidazo[4,5-b]pyrazin-2-yl and benzopyranyl. Among them, pyridyl, oxazolyl or thiazolyl group is preferable.

In the formula (I), the hydrocarbon group and heterocyclic group represented by R may optionally have 1 to 5, preferably 1 to 3 substituents at any substitutable positions. Examples of such substituents include aliphatic hydrocarbon group, alicyclic hydrocarbon group, aryl group, aromatic heterocyclic group, non-aromatic heterocyclic group, halogen atom, nitro group, optionally substituted amino group, optionally substituted acyl group, optionally substituted hydroxyl group, optionally substituted thiol group, optionally esterified carboxyl group, amidino group, carbamoyl group, sulfamoyl group, sulfo group, cyano group, azido group and nitroso group.

Examples of the aliphatic hydrocarbon groups include C_{1-15} straight-chain or branched aliphatic hydrocarbon groups as exemplified by alkyl group, alkenyl group, and alkynyl group.

Preferable examples of the alkyl group include C_{1-10} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, hexyl, pentyl, octyl, nonyl and decyl.

Preferable examples of the alkenyl group include C_{2-10} alkenyl groups such as vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl.

Preferable examples of the alkynyl group include C_{2-10} alkynyl groups such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As the alicyclic hydrocarbon group, mention is made of C_{3-12} saturated or unsaturated alicyclic hydrocarbon groups as exemplified by cycloalkyl group, cycloalkenyl group and cycloalkadienyl group.

Preferable examples of cycloalkyl group include C_{3-10} cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl and bicyclo[4.3.1]decyl.

Preferable examples of the cycloalkenyl group include C_{3-10} cycloalkenyl groups such as 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl and 3-cyclohexen-1-yl.

Preferable examples of the cycloalkadienyl group include C_{4-10} cycloalkadienyl groups such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl and 2,5-cyclohexadien-1-yl.

Preferable examples of the aryl group include C_{6-14} aryl groups such as phenyl, naphthyl (1-naphthyl, 2-naphthyl), anthryl, phenanthryl and acenaphthylenyl.

Preferable examples of the aromatic heterocyclic group include aromatic monocyclic heterocyclic groups such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl; and aromatic condensed heterocyclic groups such as benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, 1,2-benzoisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylidinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenathridinyl, phenathrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl.

Preferable examples of the non-aromatic heterocyclic group include oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidino, piperidino, morpholino and thiomorpholino.

Examples of the halogen atom include fluorine, chlorine, bromine and iodine.

As the substituted amino group in the optionally substituted amino group, mention is made of, N-monosubstituted amino group and N,N-disubstituted amino group. Examples of the substituted amino groups include amino groups having one or two substituents selected from C_{1-10} alkyl group, C_{2-10} alkenyl group, C_{2-10} alkynyl group, aromatic group, heterocyclic group and C_{1-10} acyl group (e.g. methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclohexylamino, phenylamino, N-methyl-N-phenyl-amino, acetylamino, propionylamino, benzoylamino and nicotinoylamino).

As the acyl group, mention is made of C_{1-13} acyl groups such as C_{1-10} alkanoyl group, C_{3-10} alkenoyl group, C_{4-10} cycloalkanoyl group, C_{4-10} cycloalkenoyl group and C_{6-12} aromatic carbonyl group.

Preferable examples of the C_{1-10} alkanoyl group include formyl acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl and octanoyl. Preferable examples of the C_{3-10} alkenoyl group include acryloyl, methacryloyl, crotonoyl and isocrotonoyl. Preferable examples of C_{4-10} cycloalkanoyl group include cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl and cycloheptanecarbonyl. Preferable examples of C_{4-10} cycloalkenoyl group include 2-cyclohexenecarbonyl. Preferable examples of C_{6-12} aromatic carbonyl group include benzoyl, naphthoyl and nicotinoyl.

As the substituent in the substituted acyl group, mention is made of, for example, C_{1-3} alkyl group, C_{1-3} alkoxy group, halogen atom (e.g. chlorine, fluorine, bromine, etc.), nitro group, hydroxyl group and amino group.

As the substituted hydroxyl group in the optionally substituted hydroxyl group, mention is made of, for example, alkoxy group, cycloalkyloxy group, alkenyloxy group, cycloalkenyloxy group, aralkyloxy group, acyloxy group and aryloxy group.

Preferable examples of the alkoxy group include C_{1-10} alkoxy groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, t.-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy and nonyloxy. Preferable examples of the cycloalkyloxy group include C_{3-10} cycloalkyloxy groups such as cyclobutoxy, cyclopentyloxy and cyclohexyloxy. Preferable examples of the alkenyloxy group include C_{2-10} alkenyloxy groups such as allyloxy, crotyloxy, 2-pentenyloxy and

3-hexenyloxy. Preferable examples of the cycloalkenyloxy group include C_{3-10} cycloalkenyloxy groups such as 2-cyclopentenyloxy and 2-cyclohexenyloxy. Preferable examples of the aralkyloxy group include C_{7-10} aryloxy groups such as phenyl-C_{1-4}alkyloxy (e.g. benzyloxy and phenethyloxy). Preferable examples of the acyloxy group include C_{2-13} acyloxy group, more preferably C_{2-4} alkanoyloxy groups (e.g. acetyloxy, propionyloxy, butyryloxy and isobutyryloxy). Preferable examples of the aryloxy group include C_{6-14} aryloxy groups such as phenoxy and naphthyloxy. The aryloxy group may optionally have one or two substituents such as halogen atom (e.g. chlorine, fluorine, bromine). Examples of the substituted aryloxy group include 4-chlorophenoxy.

As the substituted thiol group in the optionally substituted thiol group, mention is made of, alkylthio group, cycloalkylthio group, alkenylthio group, cycloalkenylthio group, aralkylthio group, acylthio group and arylthio group.

Preferable examples of the alkylthio group include C_{1-10} alkylthio groups such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec.-butylthio, t.-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio and nonylthio. Preferable examples of the cycloalkylthio group include C_{3-10} cycloalkylthio groups such as cyclobutylthio, cyclopentylthio and cyclohexylthio. Preferable examples of the alkenylthio group include C_{2-10} alkenylthio groups such as allylthio, crotylthio, 2-pentenylthio and 3-hexenylthio. Preferable examples of the cycloalkenylthio group include C_{3-10} cycloalkenylthio groups such as 2-cyclopentenylthio and 2-cyclohexenylthio. Preferable examples of the aralkylthio include C_{7-10} aralkylthio groups such as phenyl-C_{1-4}alkylthio (e.g. benzylthio and phenethylthio). Preferable examples of the acylthio group include C_{2-13} acylthio group, more preferably C_{2-4} alkanoylthio groups (e.g. acetylthio, propionylthio, butyrylthio and isobutyrylthio).

Preferable examples of the arylthio group include C_{6-14} arylthio groups such as phenylthio and naphthylthio. The arylthio group may optionally have one or two substituents such as halogen atom (e.g. chlorine, fluorine, bromine). Examples of the substituted arylthio group include 4-chlorophenylthio.

As the optionally esterified carboxyl group, mention is made of, for example, alkoxycarbonyl group, aralkyloxycarbonyl group and aryloxycarbonyl group.

Preferable examples of the alkoxycarbonyl group include C_{2-5} alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and butoxycarbonyl. Preferable examples of the aralkyloxycarbonyl group include C_{8-10} aralkyloxycarbonyl groups such as benzyloxycarbonyl. Preferable examples of the aryloxycarbonyl group include C_{7-15} aryloxycarbonyl groups such as phenoxycarbonyl and p-tolyloxycarbonyl.

Among the substituents on the hydrocarbon group and heterocyclic group represented by R, C_{1-10} alkyl groups, aromatic heterocyclic groups and C_{6-14} aryl groups are preferable, and C_{1-3} alkyl, furyl, thienyl, phenyl and naphthyl are especially preferable.

In the formula (I), substituents on the hydrocarbon group and heterocyclic group which are represented by R, may, when they are alicyclic hydrocarbon group, aryl group, aromatic heterocyclic group or non-aromatic heterocyclic group, have one or more, preferably 1 to 3, of suitable substituents respectively. Examples of these substituents include C_{1-6} alkyl groups, C_{2-6} alkenyl groups, C_{2-6} alkynyl groups, C_{3-7} cycloalkyl groups, C_{6-14} aryl groups, aromatic heterocyclic groups (e.g. thienyl, furyl, pyridyl, oxazolyl and thiazolyl), non-aromatic heterocyclic groups (e.g. tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolidino and piperazino), C_{7-9} aralkyl groups, amino group, N-mono-C_{1-4} alkylamino groups, N, N—di—C_{1-4} alkylamino groups, C_{2-8} acylamino groups (e.g. acetylamino, propionylamino and benzoylamino), amidino group, C_{2-8} acyl group (e.g. C_{2-8} alkanoyl groups), carbamoyl group, N-mono-C_{1-4} alkyl carbamoyl groups, N,N—di—C_{1-4} alkyl carbamoyl groups, sulfamoyl group, N-mono-C_{1-4} alkyl sulfamoyl groups, N,N—di—C_{1-4} alkyl sulfamoyl groups, carboxyl group, C_{2-6} alkoxycarbonyl groups, hydroxyl group, C_{1-4} alkoxy groups, C_{2-5} alkenyloxy groups, C_{3-7} cycloalkyloxy groups, C_{7-9} aralkyloxy groups, C_{6-14} aryloxy groups, mercapto group, C_{1-4} alkylthio groups, C_{7-9} aralkylthio groups C_{6-14} arylthio groups, sulfo group, cyano group, azido group, nitro group, nitroso group and halogen atom.

In the formula (I), R is preferably an optionally substituted heterocyclic group. R is more preferably pyridyl, oxazolyl or thiazolyl group which is optionally substituted by 1 to 3 substituents selected from C_{1-3} alkyl group, furyl group, thienyl group, phenyl group and naphthyl group.

R' in the formula (II) has the same definition as R except that R' does not represent benzopyranyl group when m and n are 0; X represents CH; A represents a bond; Q represents sulfur atom; R^1, L and M represent hydrogen atom; and ring E does not have further substituents.

In the formulae (I) and (II), Y represents —CO—, —CH(OH)— or —NR^3— (wherein R^3 represents an optionally substituted alkyl group), preferably —CH(OH)— or —NR^3—. As the alkyl group in the optionally substituted alkyl group represented by R^3, mention is made of, for example, C_{1-4} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl and t.-butyl. Examples of the substituents include halogen (e.g., fluorine, chlorine, bromine and iodine), C_{1-4} alkoxy groups (e.g. methoxy, ethoxy, propoxy, butoxy, isobutoxy, sec.-butoxy and t.-butoxy), hydroxyl group, nitro group and C_{1-4} acyl groups (e.g. formyl, acetyl and propionyl).

The symbol m is 0 or 1, preferably 0.

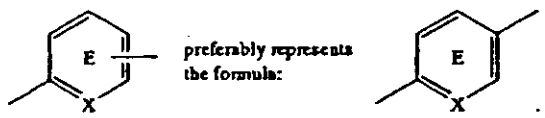
The symbol n is 0, 1 or 2, preferably 0 or 1.

X represents CH or N, preferably CH.

In the formulae (I) and (II), A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group. The aliphatic hydrocarbon group may be straight-chain or branched, and saturated or unsaturated. Specific examples of the aliphatic hydrocarbon group include saturated ones [e.g. —CH_2—, —$CH(CH_3)$—, —$(CH_2)_2$—, —$CH(C_2H_5)$—, —$(CH_2)_3$—, —$(CH_2)_4$—, —$(CH_2)_5$—, —$(CH_2)_6$— and —$(CH_2)_7$—] and unsaturated ones [e.g. —CH=CH—, —$C(CH_3)$=CH—, —CH=CH—CH_2—, —$C(C_2H_5)$=CH—, —CH_2—CH=CH—CH_2—, —CH_2—CH_2—CH=CH—CH_2—. —CH=CH—CH=CH—CH_2— and —CH=CH—CH=CH—CH=CH—CH_2—. A is preferably a bond or C_{1-4} divalent aliphatic hydrocarbon groups, the aliphatic hydrocarbon groups preferably being saturated. A is more preferably a bond or —$(CH_2)_2$—.

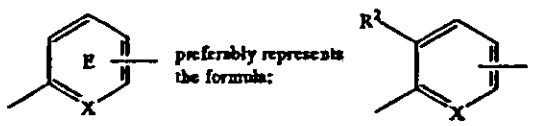
As the alkyl group represented by R^1, substantially the same one as the alkyl group in the above-mentioned R^3. R^1 is preferably hydrogen atom.

In the formulae (I) and (II), the partial formula:



Ring E has 1 to 4 substituents at any substitutable positions. Examples of such substituents include alkyl group, optionally substituted hydroxyl group, halogen atom, optionally substituted acyl group and optionally substituted amino group. These substituents have substantially the same meaning as those described as substituents of the hydrocarbon group and heterocyclic group represented by R.

Ring E, namely the partial formula:



wherein R^2 represents hydrogen atom, an alkyl group, an optionally substituted hydroxyl group, a halogen atom, an optionally substituted acyl group, nitro group or an optionally substituted amino group.

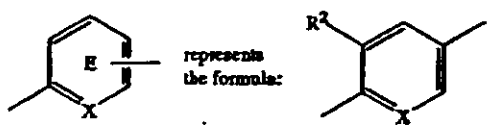
As the alkyl group, optionally substituted hydroxyl group, halogen atom, optionally substituted acyl group and optionally substituted amino group represented by R^2, mention is made of those described as substituents of the hydrocarbon group and heterocyclic group represented by R. R^2 is preferably hydrogen atom, optionally substituted hydroxyl group or halogen atom, more preferably hydrogen atom or optionally substituted hydroxyl group, especially preferably hydrogen atom or C_{1-4} alkoxy groups.

In the formulae (I) and (II), L and M represent hydrogen atom, or they may optionally be combined with each other to form a bond. L and M are preferably hydrogen atom.

In the compounds wherein L and M are combined with each other to form a bond, there exist (E)- and (Z)- isomers relative to the double bond at the 5-position of the azolidinedione ring.

And, in the compounds wherein L and M respectively represent hydrogen atom, there exist (R)- and (S)- optical isomers due to the asymmetric carbon at the 5-position of the azolidinedione ring. The compounds include these (R)- and (S)- optical isomers and racemic isomers.

Preferable examples of the compounds represented by the formula (I) or (II) includes those in which R is pyridyl, oxazolyl or thiazolyl group optionally having 1 to 3 substituents selected from C_{1-3} alkyl, furyl, thienyl, phenyl and naphthyl; m is 0; n is 0 or 1; X is CH; A is a bond or $-(CH_2)_2-$; R^1 is hydrogen atom; ring E, namely the partial formula:



and R^2 is hydrogen atom or C_{1-4} alkoxy group; and L and M are both hydrogen atom.

Preferable examples of the compound represented by the formula (I) include

(1) the compound represented by the formula (III) such as 5-[4-[2-(3-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione; 5-[4-[2-(4-ethyl-2-pyridyl)ethoxy]-benzyl]-2,4-thiazolidinedione; 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (generic name: pioglitazone); and 5-[4-[2-(6-ethyl-2-pyridyl)-ethoxy]benzyl]-2,4-thiazolidinedione;

(2) (R)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione; and

(3) 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (generic name: troglitazone/CS-045).

The compound represented by the formula (I) is especially preferably pioglitazone.

The compound represented by the formula (II) is preferably the compound represented by the formula (III) and (R)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione, more preferably pioglitazone.

The pharmacologically acceptable salt of the compound represented by the formula (I) or (II) are exemplified by salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

Preferable examples of salts with inorganic bases include salts with alkali metals such as sodium, potassium, etc., salts with alkaline earth metals such as calcium, magnesium, etc., and salts with aluminum, ammonium, etc.

Preferable examples of salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, etc.

Preferable examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.

Preferable examples of salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.

Preferable examples of salts with basic amino acids include salts with arginine, lysine, ornithine, etc., and preferable examples of salts with acidic amino acids include salts with aspartic acid, glutamic acid, etc.

The pharmacologically acceptable salt of the compound represented by the formula (III) is preferably a salt with an inorganic acid, more preferably a salt with hydrochloric acid. Especially, pioglitazone is preferably used in the form of salt with hydrochloric acid.

The compounds represented by the formula (I) or (II) or a salt thereof can be produced in accordance with, for example, methods described in JPA S55(1980)-22636(EP-A 8203), JPA S60(1985)-208980(EP-A 155845), JPA S61(1986)-286376(EP-A 208420), JPA S61(1986)-85372(EP-A 177353), JPA S61(1986)-267580(EP-A 193256), JPA H5(1993)-86057(WO 92/18501), JPA H7(1995)-82269 (EP-A 605228), JPA H7(1995)-101945(EP-A 612743), EP-A 643050, EP-A 710659, etc. or methods analogous thereto.

Insulin sensitivity enhancers include 5-[[3,4-dihydro-2-(phenylmethyl)-2H-1-benzopyran-6yl]methyl]-2,4-thiazolidinedione (generic name: englitazone) or its sodium salt;

5-[[4-[3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl]phenyl]methyl]-2,4-thiazolidinedione (generic name: darglitazone/CP-86325) or its sodium salt;

5-[2-(5-methyl-2-phenyl-4-oxazolylmethyl)benzofuran-5-ylmethyl]-2,4-oxazolidinedione (CP-92768);

5-(2-naphthalenylsulfonyl)-2,4-thiazolidinedione (AY-31637);

4-[(2-naphthalenyl)methyl]-3H-1,2,3,5-oxathiadiazol-2-oxide (AY-30711); and

5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]-methyl]-2,4-thiazolidinedione (BRL-49653), etc. in addition to compounds mentioned hereinbefore.

In the present invention, examples of the drug which is used in combination with the above-mentioned insulin sensitivity enhancer include an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor.

α-Glucosidase inhibitors are drugs which inhibit digestive enzymes such as amylase, maltase, α-dextrinase, sucrase, etc. to retard digestion of starch and sugars. Examples of the α-glucosidase inhibitors include acarbose, N-(1,3-dihydroxy-2-propyl)valiolamine (generic name; voglibose), miglitol, etc. with preferance given to voglibose.

Aldose reductase inhibitors are drugs which inhibit the first-stage rate-limitting enzyme in the polyol pathway to prevent or arrest diabetic complications. In the hyperglycemic state of diabetes, the utilization of glucose in the polyol pathway is increased and the excess sorbitol accumulated intracellularly as a consequence acts as a tissue toxin and hence evokes the onset of complications such as diabetic neuropathy, retinopathy, and nephropathy. Examples of the aldose reductase inhibitors include tolurestat; epalrestat; 3,4-dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxazine-4-acetic acid; 2,7-difluoro-spiro(9H-fluorene-9,4'-imidazolidine)-2',5'-dione (generic name: imirestat);

3-[(4-bromo-2-fluorophenyl)methyl]-7-chloro-3,4-dihydro-2,4-dioxo-1(2H)-quinazoline acetic acid (generic name: zenarestat);

6-fluoro-2,3-dihydro-2',5'-dioxo-spiro[4H-1-benzopyran-4,4'-imidazolidine]-2-carboxamide (SNK-860); zopolrestat; sorbinil; and

1-[(3-bromo-2-benzofuranyl)sulfonyl]-2,4-imidazolidinedione (M-16209), etc.

Biguanides are drugs having actions of stimulation of anaerobic glycolysis, increase of the sensitivity to insulin in the peripheral tissues, inhibition of glucose absorption from the intestine, suppression of hepatic gluconeogenesis, and inhibition of fatty acid oxidation. Examples of the biguanides include phenformin, metformin, buformin etc.

Statin compounds are drugs having actions of lowering blood cholesterol levels by inhibiting hydroxymethylglutalyl CoA (HMG—CoA) reductase. Examples of the statin compounds include pravastatin and its sodium salt, simvastatin, lovastatin, atorvastatin, fluvastatin, etc.

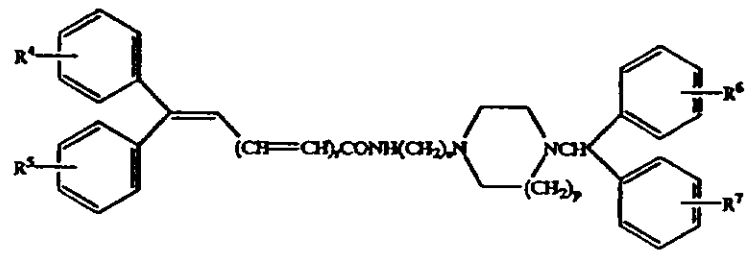
Squalene synthesis inhibitors are drugs having actions of lowering blood cholesterol levels by inhibiting synthesis of squalene. Examples of the squalene synthesis inhibitors include (S)-α-[Bis[2,2-dimethyl-1-oxopropoxy)methoxy]phosphinyl]-3-phenoxybenzenebutanesulfonic acid, mono potassium salt (BMS-188494).

Fibrate compounds are drugs having actions of lowering blood cholesterol levels by inhibiting synthesis and secretion of triglycerides in liver and activating a lipoprotein lipase.

Examples of the fibrate compounds include bezafibrate, beclobrate, binifibrate, ciplofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate, etc.

LDL catabolism enhancers are drugs having actions of lowering blood cholesterol levels by increasing the number of LDL (low-density lipoprotein) receptors.

Examples of the LDL catabolism enhancers include the compound which is described in JPA H7(1995)-316144 and represented by the formula:



wherein R^4, R^5, R^6 and R^7 are the same or different, and represent hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group; r is 0–2; s is 2–4; p is 1–2; or a salt thereof; specifically N-[2-[4-bis(4-fluorophenyl) methyl-1-piperazinyl]ethyl]-7,7-diphenyl-2,4,6-heptatrienic acid amide, etc.

The above-mentioned statin compounds, squalene synthesis inhibitors, fibrate compounds and LDL catabolism enhancers can be substituted with other drugs having the property to lower blood cholesterol and triglyceride levels. Examples of these drugs include nicotinic acid derivatives such as nicomol and niceritrol; antioxidants such as probucol; and ion-exchange resins such as colestyramin.

Angiotensin converting enzyme inhibitors are drugs having actions of partially lowering blood glucose levels as well as lowering blood pressure by inhibiting angiotensin converting enzymes. Examples of the angiotensin converting enzyme inhibitors include captopril, enalapril, alacepril, delapril, ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moveltopril, perindopril, quinapril, spirapril, temocapril, trandolapril, etc.

In the present invention, especially preferred is the pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with an α-glucosidase inhibitor. The insulin sensitivity enhancer is especially preferably pioglitazone, and the α-glucosidase inhibitor is especially preferably voglibose.

In the present invention, examples of the drug which is used in combination with the compound represented by the formula (II) or a pharmacologically acceptable salt thereof include an insulin secretion enhancer and/or an insulin preparation.

Insulin secretion enhancers are drugs having the property to promote secretion of insulin from pancreatic β cells. Examples of the insulin secretion enhancers include sulfonylureas (SU). The sulfonylureas (SU) are drugs which promote secretion of insulin from pancreatic β cells by transmitting signals of insulin secretion via SU receptors in

the cell membranes. Examples of the SU include tolbutamide; chlorpropamide; tolazamide; acetohexamide; 4-chloro-N-[(1-pyrolidinylamino)carbonyl]-benzenesulfonamide (generic name: glycopyramide) or its ammonium salt; glibenclamide (glyburide); gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; tolcyclamide, etc.

Insulin secretion enhancers include N-{[4-(1-methylethyl)cyclohexyl]carbonyl}-D-phenylalanine (AY-4166); calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl)propionate dihydrate (KAD-1229); and glimepiride (Hoe 490), etc. in addition to compounds mentioned hereinbefore. The insulin secretion enhancer is especially preferably glibenclamide.

Examples of the insulin preparations include animal insulin preparations typically extracted from bovine or porcine pancreas and human insulin preparations synthesized by genetic engineering techniques typically using *Escherichia coli* or yeasts. While insulin preparations are available in a variety of types, e.g. immediate-acting, bimodal-acting, intermediate-acting, and long-acting, these type of preparations can be selectively administered according to the patient's condition.

In the present invention, especially preferred is the pharmaceutical composition which comprises the compound represented by the formula (II) or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer. The compound represented by the formula (II) or a pharmacologically acceptable salt thereof is especially preferably pioglitazone, and the insulin secretion enhancer is especially preferably glibenclamide.

The pharmaceutical composition comprising an insulin sensitivity enhancer in combination with at least one member selected from the group consisting of an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor; and the pharmaceutical composition comprising the compound represented by the formula (II) or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation, both provided in accordance with the present invention, can be respectively put to use by mixing the respective active components either all together or independently with a physiologically acceptable carrier, excipient, binder, diluent, etc. and administering the mixture or mixtures either orally or non-orally as a pharmaceutical composition. When the active components are formulated independently, the respective formulations can be extemporaneously admixed using a diluent or the like and administered or can be administered independently of each other, either concurrently or at staggered times to the same subject.

The dosage form for said pharmaceutical composition includes such oral dosage forms as granules, powders, tablets, capsules, syrups, emulsions, suspensions, etc. and such non-oral dosage forms as injections (e.g. subcutaneous, intravenous, intramuscular and intraperitoneal injections), drip infusions, external application forms (e.g. nasal spray preparations, transdermal preparations, ointments, etc.), and suppositories (e.g. rectal and vaginal suppositories).

These dosage forms can be manufactured by the per se known technique conventionally used in pharmaceutical procedures. The specific manufacturing procedures are as follows.

To manufacture an oral dosage form, an excipient (e.g. lactose, sucrose, starch, mannitol, etc.), a dis-integrator (e.g. calcium carbonate, carboxymethylcellulose calcium, etc.), a binder (e.g. α-starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, etc.), and a lubricant (e.g. talc, magnesium stearate, polyethylene glycol 6000, etc.), for instance, are added to the active component or components and the resulting composition is compressed. Where necessary, the compressed product is coated, by the per se known technique, for masking the taste or for enteric dissolution or sustained release. The coating material that can be used includes, for instance, ethyl-cellulose, hydroxymethylcellulose, polyoxyethylene glycol, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, and Eudragit (Rohm & Haas, Germany, methacrylic-acrylic copolymer).

Injections can be manufactured typically by the following procedures. The active component or components are dissolved, suspended or emulsified in an aqueous vehicle (e.g. distilled water, physiological saline, Ringer's solution, etc.) or an oily vehicle (e.g. vegetable oil such as olive oil, sesame oil, cottonseed oil, corn oil, etc. or propylene glycol) together with a dispersant (e.g. Tween 80 (Atlas Powder, U.S.A.), HCO 60 (Nikko Chemicals), polyethylene glycol, carboxymethylcellulose, sodium alginate, etc.), a preservative (e.g. methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, benzyl alcohol, chlorobutanol, phenol, etc.), an isotonizing agent (e.g. sodium chloride, glycerol, sorbitol, glucose, inverted sugar, etc.) and other additives. If desired, a solubilizer (e.g. sodium salicylate, sodium acetate, etc.), a stabilizer (e.g. human serum albumin), a soothing agent (e.g. benzalkonium chloride, procaine hydrochloride, etc.) and other additives can also be added.

A dosage form for external application can be manufactured by processing the active component or components into a solid, semi-solid or liquid composition. To manufacture a solid composition, for instance, the active component or components, either as they are or in admixture with an excipient (e.g. lactose, mannitol, starch, microcrystalline cellulose, sucrose, etc.), a thickener (e.g. natural gums, cellulose derivatives, acrylic polymers, etc.), etc., are processed into powders. The liquid composition can be manufactured in substantially the same manner as the injections mentioned above. The semi-solid composition is preferably provided in a hydrous or oil gel form or an ointment form. These compositions may optionally contain a pH control agent (e.g. carbonic acid, phosphoric acid, citric acid, hydrochloric acid, sodium hydroxide, etc.), and a preservative (e.g. p-hydroxybenzoic acid esters, chlorobutanol, benzalkonium chloride, etc.), among other additives.

Suppositories can be manufactured by processing the active component or components into an oily or aqueous composition, whether solid, semi-solid or liquid. The oleaginous base that can be used includes, for instance, higher fatty acid glycerides [e.g. cacao butter, Witepsols (Dinamit-Nobel), etc.], medium-chain fatty acids [e.g. Migriols (Dinamit-Nobel), etc.], vegetable oils (e.g. sesame oil, soybean oil, cottonseed oil, etc.), etc. The water-soluble base includes, for instance, polyethylene glycols, propylene glycol, etc. The hydrophilic base includes, for instance, natural gums, cellulose derivatives, vinyl polymers, and acrylic polymers, etc.

The pharmaceutical composition of the present invention is low in toxicity and can be safely used in mammals (e.g. humans, mice, rats, rabbits, dogs, cats, bovines, horses, swines, monkeys).

The dosage of the pharmaceutical composition of the present invention may be appropriately determined with reference to the dosages recommended for the respective

active components and can be selected appropriately according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of the active components, among other factors. For example, the dosage of the insulin sensitivity enhancer for an adult can be selected from the clinical oral dose range of 0.01 to 10 mg/kg body weight (preferably 0.05 to 10 mg/kg body weight, more preferably 0.05 to 5 mg/kg body weight) or the clinical parenteral dose range of 0.005 to 10 mg/kg body weight (preferably 0.01 to 10 mg/kg body weight, more preferably 0.01 to 1 mg/kg body weight). The other active component or components having different modes of action for use in combination can also be used in dose ranges selected by referring to the respective recommended clinical dose ranges. The preferred frequency of administration is 1 to 3 times a day.

The proportions of the active components in the pharmaceutical composition of the present invention can be appropriately selected according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of active components, among other factors. When, for example, the compound represented by the formula (I) or a pharmacologically acceptable salt thereof (e.g. pioglitazone) which is the insulin sensitivity enhancer and voglibose which is an α-glucosidase inhibitor are to be administered in combination to a human subject, voglibose is used in a proportion of usually about 0.0001 to 0.2 weight parts and preferably about 0.001 to 0.02 weight parts relative to 1 weight part of the compound or a salt thereof. When, for example, the compound represented by the formula (II) or a pharmacologically acceptable salt thereof and glibenclamide which is an insulin secretion enhancer are to be administered in combination to a human subject, glibenclamide is used in a proportion of usually about 0.002 to 5 weight parts and preferably about 0.025 to 0.5 weight parts, relative to 1 weight part of the compound or a pharmacologically acceptable salt thereof.

The pharmaceutical composition of the present invention shows a marked synergistic effect compared with administration of either active component alone. For example, compared with cases in which each of these active components was administered to diabetic Wistar fatty rats with genetical obesity, administration of these active components in combination resulted in marked improvements in both hypoglycemia and reduced glucose tolerance. Thus, the pharmaceutical composition of the present invention lowers blood glucose in diabetics more effectively than it is the case with administration of each component drug alone and, therefore, can be used advantageously for the prophylaxis and treatment of diabetic complications.

Furthermore, since the pharmaceutical composition of the present invention develops sufficient efficacy with reduced doses as compared with the administration of any one of the active components alone, the side effects of the respective components (e.g. gastrointestinal disorders such as diarrhea, etc.) can be reduced.

The following working examples and experimental examples are merely intended to illustrate the present invention in further detail but should by no means be construed as defining the scope of the invention.

The pharmaceutical composition of the present invention can be prepared according to the following formulations.

WORKING EXAMPLE 1

Capsules

(1) Pioglitazone hydrochloride	30 mg
(2) Voglibose	0.2 mg
(3) Lactose	60 mg
(4) Microcrystalline cellulose	79.8 mg
(5) Magnesium stearate	10 mg
Total	180 mg

The whole amounts of (1), (2), (3) and (4) and half the amount of (5) are mixed well and granulated in the conventional manner. Then, the balance of (5) is added and, after mixing, the whole composition is filled in a gelatin hard capsule shell.

WORKING EXAMPLE 2

(1) Pioglitazone hydrochloride	10 mg
(2) Glibenclamide	1.25 mg
(3) Lactose	86.25 mg
(4) Corn starch	20 mg
(5) Polyethylene glycol	2.5 mg
(6) Hydroxypropylcellulose	4 mg
(7) Carmellose calcium	5.5 mg
(8) Magnesium stearate	0.5 mg
	130 mg (per tablet)

The whole amounts of (1), (2), (3), (4), and (5), ⅔ amounts of (6) and (7), and ½ amount of (8) are mixed well and granulated in the conventional manner. Then, the balances of (6), (7) and (8) are added to the granules, which is mixed well and the whole composition is compressed with a tablet machine. The adult dosage is 3 tablets/day, to be taken in 1 to 3 divided doses.

WORKING EXAMPLE 3

Capsules

(1) Pioglitazone hydrochloride	10 mg
(2) Epalrestat	50 mg
(3) Lactose	55 mg
(4) Microcrystalline cellulose	55 mg
(5) Magnesium stearate	10 mg
Total	180 mg

The whole amounts of (1), (2), (3) and (4) and ½ amount of (5) are mixed well and granulated in the conventional manner. Then, the balance of (5) is added and the whole composition is filled in gelatin capsule shell. The adult dosage is 3 capsules/day, to be taken in 1 to 3 doses.

EXPERIMENTAL EXAMPLE 1

Effect of pioglitazone hydrochloride in combination with α-glucosidase inhibitor in genetically obese and diabetic Wistar fatty rats

Male Wistar fatty rats aged 14–19 weeks were divided into 4 groups of 5–6, and pioglitazone hydrochloride (1 mg/kg body wt./day, p.o.) and/or voglibose (an

α-glucosidase inhibitor) (0.31 mg/kg body wt./day; administered by mixing in commercial diet at a rate of 5 ppm) was administered for 14 days. The blood was then collected from the tail vein and the plasma glucose and hemoglobin A_1 were determined by the enzymatic method (Encore Chemical System, Baker) and using a commercial kit (NC-ROPET, Nippon Chemiphar Co.), respectively. The results were expressed in mean±standard deviation for each group (n=5–6) and analyzed by Dunnett's test, which are shown in Table 1. The 1% level of significance was used.

TABLE 1

Group	Plasma glucose (mg/dl)	Hemoglobin A_1 (%)
Control	345 ± 29	5.7 ± 0.4
Pioglitazone	215 ± 50*	5.2 ± 0.3
Voglibose	326 ± 46	6.0 ± 0.6
Pioglitazone + voglibose	114 ± 23*	4.5 ± 0.4*

*P < 0.01 vs. control group

It is apparent from Table 1 that both the blood glucose and hemoglobin A_1 levels were remarkably lowered by combined administration of pioglitazone and voglibose as compared with the administration of either drug alone.

EXPERIMENTAL EXAMPLE 2

Effect of pioglitazone hydrochloride in combination with an insulin secretion enhancer in genetically obese and diabetic Wistar fatty rats

Male Wistar fatty rats aged 13–14 weeks were divided into 4 groups of 5, and pioglitazone hydrochloride (3 mg/kg/day, p.o.) and/or glibenclamide (an insulin secretion enhancer) (3 mg/kg/day, p.o.) was administered for 7 days. Following an overnight fast, the oral glucose loading test (2 g glucose/kg/5 ml, p.o.) was carried out. Prior to glucose loading and 120 and 240 minutes after the loading, blood was collected from the tail vein and the plasma glucose was assayed by the enzymatic method (Encore Chemical System, Baker). The results were expressed in mean±SD for each group (n=5) and analyzed by Dunnett's test, which are shown in Table 2.

TABLE 2

Group	Plasma glucose (mg/dl) 0 min.	120 min.	240 min.
Control	119 ± 9	241 ± 58	137 ± 10
Pioglitazone	102 ± 12	136 ± 17*	102 ± 19*
Glibenclamide	118 ± 12	222 ± 61	106 ± 24*
Pioglitazone + glibenclamide	108 ± 3	86 ± 10*	60 ± 5*

*P < 0.01 vs. control group

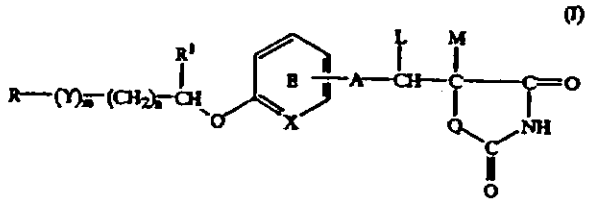
It is apparent from Table 2 that the increase of blood sugar following glucose loading was remarkably inhibited by the combined administration of pioglitazone and glibenclamide as compared with the administration of either drug alone.

The pharmaceutical composition of the present invention shows a potent depressive effect on diabetic hyperglycemia and is useful for prophylaxis and treatment of diabetes. Moreover, this pharmaceutical composition is useful for prophylaxis and treatment of diabetic complications such as diabetic neuropathy, nephropathy, retinopathy, macroangiopathy, and osteopenia. In addition, by appropriately selecting the kinds of component drugs, administration route, dosage, etc. according to clinical status, stable hypoglycemic efficacy in long-term therapy can be expected with an extremely low risk of side effect.

What is claimed is:

1. A method for reducing the side effects of active components administered to a diabetic patient, which comprises administering to said patient a therapeutically effective amount of an insulin sensitivity enhancer in combination with a biguanide as said active components.

2. The method according to claim 1, wherein the insulin sensitivity enhancer is a compound represented by the formula:



(I)

wherein R represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR^3— wherein R^3 represents an optionally substituted alkyl group; m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R^1 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 further substituents, and the substituents may optionally be combined with R^1 to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; or a pharmacologically acceptable salt thereof.

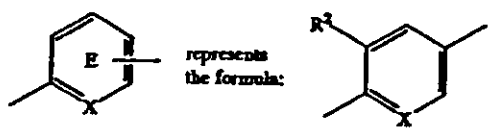
3. The method according to claim 2, wherein R is an optionally substituted heterocyclic group.

4. The method according to claim 2, wherein m is 0.

5. The method according to claim 2, wherein X is CH.

6. The method according to claim 2, wherein R^1 is hydrogen atom.

7. The method according to claim 2, wherein the partial formula:

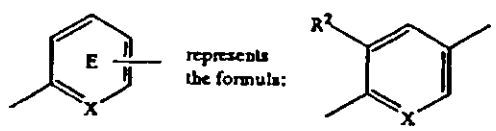


represents the formula:

wherein R^2 represents hydrogen atom, an alkyl group, an optionally substituted hydroxyl group, a halogen atom, an optionally substituted acyl group, nitro group or an optionally substituted amino group.

8. The method according to claim 2, wherein L and M are hydrogen atoms.

9. The method according to claim 2, wherein R is pyridyl, oxadolyl or thiazolyl group optionally having 1 to 3 substituents selected from C_{1-3} alkyl, furyl, thienyl, phenyl and naphthyl; m is 0; n is 0 or 1; X is CH; A is a bond or —$(CH_2)_2$—; R^1 is hydrogen atom; where in partial formula:



and wherein R^2 is hydrogen atom or C_{1-4} alkoxy group; and L and M are both hydrogen atoms.

10. The method according to claim 2, wherein the compound represented by the formula (I) is pioglitazone or its hydrochloride.

11. The method according to claim 1, wherein the biguanide is selected from the group consisting of phenformin, metformin and buformin.

12. The method according to claim 1, wherein the biguanide is metformin.

13. The method according to claim 1, wherein the insulin sensitivity enhancer is pioglitazone or its hydrochloride and the biguanide is metformin.

14. The method according to claim 1, wherein the insulin sensitivity enhancer is troglitazone.

15. The method according to claim 1, wherein the insulin sensitivity enhancer is 5-[[4-[2-(methyl-2-pyridylamino) ethoxy]phenyl]-methyl]-2,4-thiazolidinedione or its pharmacologically acceptable salt.

16. The method according to claim 1, wherein the insulin sensitivity enhancer and biguanide are mixed together to form an admixture and the admixture is administered to the mammal.

17. The method according to claim 1, wherein the insulin sensitivity enhancer and biguanide are not mixed together but are administered independently to the mammal.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,172,090 B1
DATED : January 9, 2001
INVENTOR(S) : Hitoshi Ikeda et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 18,
Line 64, change "oxadolyl" to -- oxazolyl --;
Line 67, change "where in" to -- wherein --.

Signed and Sealed this

Eighteenth Day of December, 2001

Attest:

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

Attesting Officer

US006211205B1

(12) **United States Patent**
Ikeda et al.

(10) **Patent No.: US 6,211,205 B1**
(45) **Date of Patent: Apr. 3, 2001**

(54) **PHARMACEUTICAL COMPOSITION**

(75) Inventors: **Hitoshi Ikeda, Higashiosaka; Takashi Sohda, Takatsuki; Hiroyuki Odaka, Kobe, all of (JP)**

(73) Assignee: **Takeda Chemical Industries, Ltd., Osaka (JP)**

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/606,176**

(22) Filed: **Jun. 29, 2000**

Related U.S. Application Data

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(51) Int. Cl.[7] C07D 401/02; A61K 31/44; A61K 31/42; A61K 31/425

(52) U.S. Cl. 514/342; 514/340; 514/369; 514/370; 546/269.7; 546/271.4; 548/183; 548/227

(58) Field of Search 546/269.7, 271.4; 548/183, 227; 514/340, 342, 369, 376

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(List continued on next page.)

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(57) **ABSTRACT**

Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with other antidiabetics differing from the enhancer in the mechanism of action, which shows a potent depressive effect on diabetic hyperglycemia and is useful for prophylaxis and treatment of diabetes.

12 Claims, No Drawings

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PHARMACEUTICAL COMPOSITION

FIELD OF THE INVENTION

This application is a divisional of pending application U.S. Ser. No. 09/280,710, filed Mar. 30, 1999, now allowed which is a divisional of U.S. Ser. No. 09/057,465, filed Apr. 9, 1998, now U.S. Pat. No. 5,965,584, which is a divisional of application Ser. No. 08/667,979, filed Jun. 19, 1996, now U.S. Pat. No. 5,952,356.

BACKGROUND OF THE INVENTION

The present invention relates to a pharmaceutical composition comprising an insulin sensitivity enhancer in combination with one or more other antidiabetics differing from said enhancer in the mechanism of action.

Recent years, the pathology of diabetes has become more and more understood and, in parallel, drugs specific for the respective pathologic states have been developed Accordingly a variety of drugs having new mechanisms of action have appeared one after-another.

Insulin sensitivity enhancers are also known as insulin resistance deblockers because they have the action to normalize the impaired insulin receptor function, and are gathering much attention in these years.

Regarding such insulin sensitivity enhancers, a very useful compound such as pioglitazone has been developed [Pujita et al., Diabetes, 32, 804–810, 1983, JP-A S55(1980)-22636 (EP-A 8203), JP-A S61(1986)-267580 (EP-A 193256)]. Pioglitazone restores the impaired insulin receptor function to normalize the uneven distribution of glucose transporters in cells, the cardinal enzyme systems associated with glycometabolism, such as glucokinase, and enzyme systems associated with lipidmetabolism, such as lipoprotein lipase. As the results, insulin resistance are deblocked to improve glucose tolerance, and lower the plasma concentrations of neutral lipids and free fatty acids. Since these actions of pioglitazone are comparatively gradual and the risk of side effect in long-term administration is also low, this compound is useful for obese patients who are presumed to be highly insulin-resistant.

Also, insulin sensitivity enhancers such as CS-045, thiazolidinedione derivatives and substituted thiazolidinedione derivatives are reported to be used in combination with insulin [JP-A H4(1992)-66579, JP-A H4(1992)-69383, JP-A H5(1993)-202042]. However, the pharmaceutical composition having a specific combination of the present invention is unknown.

Diabetes is a chronic disease with diverse pathologic manifestations and is accompanied by lipidmetabolism disorders and circulatory disorders as well as glycometabolism disorders. As the results, diabetes tends to progress entailing various complications in many cases. Therefore, it is necessary to select the drug of choice for the prevailing disease state in each individual case. However, this selection is often difficult in clinical settings because single use of each individual drug can not bring sufficient effects in some disease states and there are various problems such as side effect which is caused by an increased dose or a long-term administration.

SUMMARY OF THE INVENTION

In view of the above state of the art, the inventors of the present invention did much research to develop antidiabetics which would not virtually cause adverse reactions even on long-term administration and could be effective for a large

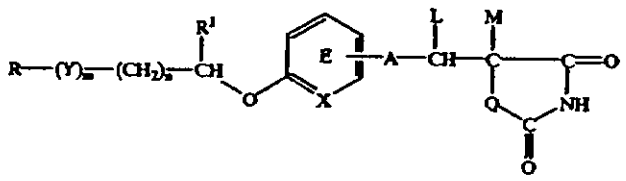
cohort of the diabetic population. As a consequence, they discovered that the above object can be accomplished by using an insulin sensitivity enhancer, such as the drug described above, in combination with other antidiabetics differing from said enhancer in the mechanism of action, and accordingly have perfected the present invention.

The present invention, therefore, relates to:

1) Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with at least one member of the group consisting of an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor;

2) Pharmaceutical composition according to 1), wherein the insulin sensitivity enhancer is a compound represented by the formula:

(I)



wherein R represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR^3— (wherein R^3 represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R^1 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 substituents, and the substituents may optionally be combined with R^1 to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; or a pharmacologically acceptable salt thereof;

3) Pharmaceutical composition according to 2), wherein the compound represented by the formula (I) is pioglitazone;

4) Pharmaceutical composition according to 1), which comprises an insulin sensitivity enhancer in combination with an α-glucosidase inhibitor;

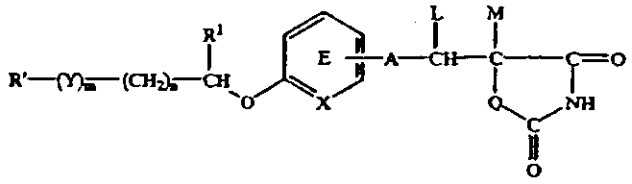
5) Pharmaceutical composition according to 4), wherein the α-glucosidase inhibitor is voglibose;

6) Pharmaceutical composition according to 4), wherein the insulin sensitivity enhancer is pioglitazone and the α-glucosidase inhibitor is voglibose;

7) Pharmaceutical composition according to 1), which is for prophylaxis or treatment of diabetes;

8) Pharmaceutical composition which comprises a compound represented by the formula:

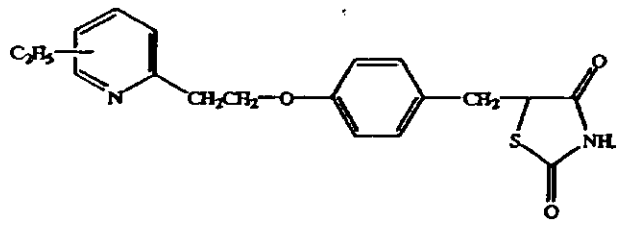
(II)



wherein R' represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR³— (wherein R³ represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R¹ represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 substituents, and the substituents may optionally be combined with R¹ to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; with a proviso that R' does not represent benzopyranyl group when m and n are 0, X represents CH, A represents a bond, Q represents sulfur atom, R¹, L and N represent hydrogen atom and ring E does not have further substituents; or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation;

9) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is the compound represented by the formula:

(III)



10) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is pioglitazone;

11) Pharmaceutical composition according to 8), wherein the insulin secretion enhancer is glibenclamide;

12) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is pioglitazone and the insulin secretion enhancer is glibenclamide;

13) Pharmaceutical composition according to 8), which is for prophylaxis or treatment of diabetes.

DETAILED DESCRIPTION OF THE INVENTION

The term "insulin sensitivity enhancer" as used in this specification means any and all drug substances that restore the impaired insulin receptor function to deblock insulin resistance and consequently enhance insulin sensitivity. As examples of the insulin sensitivity enhancer, the compound represented by the formula (I) or a pharmacologically acceptable salt thereof can be mentioned.

In the formula (I), as the hydrocarbon group in the optionally substituted hydrocarbon group represented by R,

mention is made of aliphatic hydrocarbon groups, alicyclic hydrocarbon groups, alicyclic-aliphatic hydrocarbon groups, aromatic aliphatic hydrocarbon groups and aromatic hydrocarbon groups. Number of carbon atoms in these hydrocarbon groups is preferably 1 to 14.

The aliphatic hydrocarbon groups are preferably those having 1 to 8 carbon atoms. As the aliphatic hydrocarbon groups, mention is made of C_{1-8} saturated aliphatic hydrocarbon groups (e.g. alkyl group) as exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, hexyl, isohexyl, heptyl and octyl, and C_{2-8} unsaturated aliphatic hydrocarbon groups (e.g. alkenyl group, alkadienyl group, alkynyl group, alkadiynyl group) as exemplified by vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptynyl and 1-octynyl.

The alicyclic hydrocarbon groups are preferably those having 3 to 7 carbon atoms. As the alicyclic hydrocarbon groups, mention is made of C_{3-7} saturated alicyclic hydrocarbon groups (e.g. cycloalkcyl group) as exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and C_{5-7} unsaturated alicyclic hydrocarbon groups (e.g. cycloalkenyl group, cycloalkadienyl group) as exemplified by 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl and 2,4-cycloheptadienyl.

As the alicyclic-aliphatic hydrocarbon groups, mention is made of, among those formed by combination of the above-mentioned alicyclic hydrocarbon groups with aliphatic hydrocarbon groups (e.g. cycloalkyl-alkyl group, cycloalkcenyl-alkyl group), ones having 4 to 9 carbon atoms as exemplified by cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl and cycloheptylethyl.

The aromatic aliphatic hydrocarbon groups are preferably those having 7 to 13 carbon atoms (e.g. aralkyl group). As the aromatic aliphatic hydrocarbon groups, mention is made of C_{7-9} phenylalkyl as exemplified by benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and 1-phenylpropyl, and C_{11-13} naphthylalkyl as exemplified by α-naphthylmethyl, α-naphthylethyl, β-naphthylmethyl and β-naphthylethyl.

As the aromatic hydrocarbon groups, mention is made of, ones having 6 to 14 carbon atoms as exemplified by phenyl, naphthyl (α-naphtyl, β-naphthyl).

In the formula (I), as the heterocyclic group in the optionally substituted heterocyclic group represented by R, mention is made of, for example, 5- to 7-membered heterocyclic groups containing, as a ring component atom, 1 to 4 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom, and a condensed ring group. As the condensed ring, mention is made of, for example, these 5- to 7-membered heterocyclic groups condensed with 6-membered ring containing one or two nitrogen atoms, benzene ring or 5-membered ring containing one sulfur atom.

Examples of these heterocyclic groups include 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, 1H-indazol-3-yl, 1H-pyrrolo [2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 1H-imidazo[4,5-b]pyrazin-2-yl and benzopyranyl. Among them, pyridyl, oxazolyl or thiazolyl group is preferable.

In the formula (I), the hydrocarbon group and heterocyclic group represented by R may optionally have 1 to 5, preferably 1 to 3 substituents at any substitutable positions. Examples of such substituents include aliphatic hydrocarbon group, alicyclic hydrocarbon group, aryl group, aromatic heterocyclic group, non-aromatic heterocyclic group, halogen atom, nitro group, optionally substituted amino group, optionally substituted acyl group, optionally substituted hydroxyl group, optionally substituted thiol group, optionally esterified carboxyl group, amidino group, carbamoyl group, sulfamoyl group, sulfo group, cyano group, azido group and nitroso group.

Examples of the aliphatic hydrocarbon groups include C_{1-15} straight-chain or branched aliphatic hydrocarbon groups as exemplified by alkyl group, alkenyl group, and alkynyl group.

Preferable examples of the alkyl group include C_{1-10} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, hexyl, pentyl, octyl, nonyl and decyl.

Preferable examples of the alkenyl group include C_{2-10} alkenyl groups such as vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl.

Preferable examples of the alkynyl group include C_{2-10} alkynyl groups such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As the alicyclic hydrocarbon group, mention is made of C_{3-12} saturated or unsaturated alicyclic hydrocarbon groups as exemplified by cycloalkyl group, cycloalkenyl group and cycloalkadienyl group.

Preferable examples of cycloalkenyl group include C_{3-10} cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo [2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1] nonyl and bicyclo[4.3.1]decyl.

Preferable examples of the cycloalkenyl group include C_{3-10} cycloalkenyl groups such as 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl and 3-cyclohexen-1-yl.

Preferable examples of the cycloalkadienyl group include C_{4-10} cycloalkadienyl groups such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl and 2,5-cyclohexadien-1-yl.

Preferable examples of the aryl group include C_{6-14} aryl groups such as phenyl, naphthyl (1-naphthyl, 2-naphthyl), anthryl, phenanthryl and acenaphthylenyl.

Preferable examples of the aromatic heterocyclic group include aromatic monocyclic heterocyclic groups such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl; and aromatic condensed heterocyclic groups such as benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, 1,2-benzoisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylidinyl, purinyl, pteridinyl, carbazolyl, α-carbazolyl, β-carbazolyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenathridinyl, phenathrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a] pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo [4,3-b]pyridazinyl.

Preferable examples of the non-aromatic heterocyclic group include oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidino, piperidino, morpholine and thiomorpholino.

Examples of the halogen atom include fluorine, chlorine, bromine and iodine.

As the substituted amino group in the optionally substituted amino group, mention is made of, N-monosubstituted amino group and N,N-disubstituted amino group. Examples of the substituted amino groups include amino groups having one or two substituents selected from C_{1-10} alkyl group, C_{2-10} alkenyl group, C_{2-10} alkynyl group, aromatic group, heterocyclic group and C_{1-10} acyl group (e.g. methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclohexylamino, phenylamino, N-methyl-N-phenyl-amino, acetylamino, propionylamino, benzoylamino and nicotinoylamino).

As the acyl group, mention is made of C_{1-13} acyl groups such as C_{1-10} alkanoyl group, C_{3-10} alkenoyl group, C_{4-10} cycloalkanoyl group, C_{4-10} cycloalkenoyl group and C_{6-12} aromatic carbonyl group.

Preferable examples of the C_{1-10} alkanoyl group include formyl acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl and octanoyl. Preferable examples of the C_{3-10} alkenoyl group include acryloyl, methacryloyl, crotonoyl and isocrotonoyl. Preferable examples of C_{4-10} cycloalkanoyl group include cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl and cycloheptanecarbonyl. Preferable examples of C_{4-10} cycloalkenoyl group include 2-cyclohexenecarbonyl. Preferable examples of C_{6-12} aromatic carbonyl group include benzoyl, naphthoyl and nicotinoyl.

As the substituent in the substituted acyl group, mention is made of, for example, C_{1-3} alkyl group, C_{1-3} alkoxy group, halogen atom (e.g. chlorine, fluorine, bromine, etc.), nitro group, hydroxyl group and amino group.

As the substituted hydroxyl group in the optionally substituted hydroxyl group, mention is made of, for example, alkoxy group, cycloalkyloxy group, alkenyloxy group, cycloalkenyloxy group, aralkyloxy group, acyloxy group and aryloxy group.

Preferable examples of the alkoxy group include C_{1-10} alkoxy groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, t.-butoxy pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy and nonyloxy. Preferable examples of the cycloalkyloxy group include C_{3-10} cycloalkyloxy groups such as cyclobutoxy, cyclopentyloxy and cyclohexyloxy. Preferable examples of the alkenyloxy group include C_{2-10} alkenyloxy groups such as allyloxy, crotyloxy, 2-pentenyloxy and 3-hexenyloxy. Preferable examples of the cycloalkenyloxy group include C_{3-10} cycloalkenyloxy groups such as 2-cyclopentenyloxy and 2-cyclohexenyloxy. Preferable examples of the aralkyloxy group include C_{7-10} aryloxy groups such as phenyl-C_{1-4}alkyloxy (e.g. benzyloxy and phenethyloxy). Preferable examples of the acyloxy group include C_{2-13} acyloxy group, more preferably C_{2-4} alkanoyloxy groups (e.g. acetyloxy, propionyloxy, butyryloxy and isobutyryloxy). Preferable examples of the aryloxy group include C_{6-14} aryloxy groups such as phenoxy and naphthyloxy. The aryloxy group may optionally have one or two substituents such as halogen atom (e.g. chlorine, fluorine, bromine). Examples of the substituted aryloxy group include 4-chlorophenoxy.

As the substituted thiol group in the optionally substituted thiol group, mention is made of, alkylthio group, cycloalkylthio group, alkenylthio group, cycloalkenylthio group, aralkylthio group, acylthio group and arylthio group.

Preferable examples of the alkylthio group include C_{1-10} alkylthio groups such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec.-butylthio, t.-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio and nonylthio. Preferable examples of the cycloalkylthio group include C_{3-10} cycloalkylthio groups such as cyclobutylthio, cyclopentylthio and cyclohexylthio. Preferable examples of the alkenylthio group include C_{2-10} alkenylthio groups such as allylthio, crotylthio, 2-pentenylthio and 3-hexenylthio. Preferable examples of the cycloalkenylthio group include C_{3-10} cycloalkenylthio groups such as 2-cyclopentenylthio and 2-cyclohexenylthio. Preferable examples of the aralkylthio include C_{7-10} aralkylthio groups such as phenyl-C_{1-4}alkylthio (e.g. benzylthio and phenethylthio). Preferable examples of the acylthio group include C_{2-13} acylthio group, more preferably C_{2-4} alkanoylthio groups (e.g. acetylthio, propionylthio, butyrylthio and isobutyrylthio).

Preferable examples of the arylthio group include C_{6-14} arylthio groups such as phenylthio and naphthylthio. The arylthio group may optionally have one or two substituents such as halogen atom (e.g. chlorine, fluorine, bromine). Examples of the substituted arylthio group include 4-chlorophenylthio.

As the optionally esterified carboxyl group, mention is made of, for example, alkoxycarbonyl group, aralkyloxycarbonyl group and aryloxycarbonyl group.

Preferable examples of the alkoxycarbonyl group include C_{2-5} alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and butoxycarbonyl. Preferable examples of the aralkyloxycarbonyl group include C_{8-10} aralkyloxycarbonyl groups such as benzyloxycarbonyl. Preferable examples of the aryloxycarbonyl group include C_{7-15} aryloxycarbonyl groups such as phenoxycarbonyl and p-tolyloxycarbonyl.

Among the substituents on the hydrocarbon group and heterocyclic group represented by R, C_{1-10} alkyl groups, aromatic heterocyclic groups and C_{6-14} aryl groups are preferable, and C_{1-3} alkyl, furyl, thienyl, phenyl and naphthyl are especially preferable.

In the formula (I), substituents on the hydrocarbon group and heterocyclic group which are represented by R, may, when they are alicyclic hydrocarbon group, aryl group, aromatic heterocyclic group or non-aromatic heterocyclic group, have one or more, preferably 1 to 3, of suitable substituents respectively. Examples of these substituents include C_{1-6} alkyl groups, C_{2-6} alkenyl groups, C_{2-6} alkynyl groups, C_{3-7} cycloalkyl groups, C_{6-14} aryl groups, aromatic heterocyclic groups (e.g. thienyl, furyl, pyridyl, oxazolyl and thiazolyl), non-aromatic heterocyclic groups (e.g. tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolidino and piperazino), C_{7-9} aralkyl groups, amino group, N-mono-C_{1-4}alkylamino groups, N,N-di-C_{1-4} alkylamino groups, C_{2-8} acylamino groups (e.g. acetylamino, propionylamino and benzoylamino), amidino group, C_{2-8} acyl group (e.g. C_{2-8} alkanoyl groups), carbamoyl group, N-mono-C_{1-4} alkyl carbamoyl groups, N,N-di-C_{1-4} alkyl carbamoyl groups, sulfamoyl group, N-mono-C_{1-4} alkyl sulfamoyl groups, N,N-di-C_{1-4} alkyl sulfamoyl groups, carboxyl group, C_{2-8} alkoxycarbonyl groups, hydroxyl group, C_{1-4} alkoxy groups, C_{2-5} alkenyloxy groups, C_{3-7} cycloalkyloxy groups, C_{7-9} aralkyloxy groups, C_{6-14} aryloxy groups, mercapto group, C_{1-4} alkylthio groups, C_{7-9} aralkylthio groups C_{6-1}, arylthio groups, sulfo group, cyano group, azido group, nitro group, nitroso group and halogen atom.

In the formula (I), R is preferably an optionally substituted heterocyclic group. R is more preferably pyridyl, oxazolyl or thiazolyl group which is optionally substituted by 1 to 3 substituents selected from C_{1-3} alkyl group, furyl group, thienyl group, phenyl group and naphthyl group.

R' in the formula (II) has the same definition as R except that R' does not represent benzopyranyl group when m and n are 0; X represents CH; A represents a bond; Q represents sulfur atom; R^1, L and M represent hydrogen atom; and ring E does not have further substituents.

In the formulae (I) and (II), Y represents —CO—, —CH(OH)— or —NR^3— (wherein R^3 represents an optionally substituted alkyl group), preferably —CH(OH)— or —NR^3—. As the alkyl group in the optionally substituted alkyl group represented by R^3, mention is made of, for example, C_{1-4} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl and t.-butyl. Examples of the substituents include halogen (e.g., fluorine, chlorine, bromine and iodine), C_{1-4} alkoxy groups (e.g. methoxy, ethoxy, propoxy, butoxy, isobutoxy, sec.-butoxy and t.-butoxy), hydroxyl group, nitro group and C_{1-4} acyl groups (e.g. formyl, acetyl and propionyl).

The symbol m is 0 or 1, preferably 0.

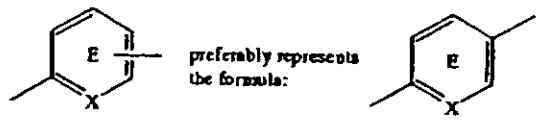
The symbol n is 0, 1 or 2, preferably 0 or 1.

X represents CH or N, preferably CH.

In the formulae (I) and (II), A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group. The aliphatic hydrocarbon group may be straight-chain or branched, and saturated or unsaturated. Specific examples of the aliphatic hydrocarbon group include saturated ones [e.g. —CH_2—, —$CH(CH_3)$—, —$(CH_2)_2$—, —$CH(C_2H_5)$—, —$(CH_2)_3$—, —$(CH_2)_4$—, —$(CH_2)_5$—, —$(CH_2)_6$— and —$(CH_2)_7$—] and unsaturated ones [e.g. —CH=CH—, —$C(CH_3)$=CH—, —CH=CH—CH_2—, —$C(C_2H_5)$=CH—, —CH_2—CH=CH—CH_2—, —CH_2—CH_2—CH=CH—CH_2—. —CH=CH—CH=CH—CH_2— and —CH=CH—CH=CH—CH=CH—CH_2—. A is preferably a bond or C_{1-4} divalent aliphatic hydrocarbon groups, the aliphatic hydrocarbon groups preferably being saturated. A is more preferably a bond or —$(CH_2)_2$—.

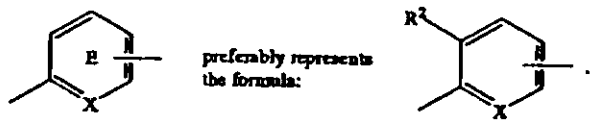
As the alkyl group represented by R^1 substantially the same one as the alkyl group in the above-mentioned R^3. R^1 is preferably hydrogen atom.

In the formulae (I) and (II), the partial formula:



Ring E has 1 to 4 substituents at any substitutable positions. Examples of such substituents include alkyl group, optionally substituted hydroxyl group, halogen atom, optionally substituted acyl group and optionally substituted amino group. These substituents have substantially the same meaning as those described as substituents of the hydrocarbon group and heterocyclic group represented by R.

Ring E, namely the partial formula:



wherein R^2 represents hydrogen atom, an alkyl group, an optionally substituted hydroxyl group, a halogen atom, an optionally substituted acyl group, nitro group or an optionally substituted amino group.

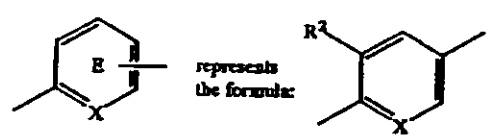
As the alkyl group, optionally substituted hydroxyl group, halogen atom, optionally substituted acyl group and optionally substituted amino group represented by R^2, mention is made of those described as substituents of the hydrocarbon group and heterocyclic group represented by R. R^2 is preferably hydrogen atom, optionally substituted hydroxyl group or halogen atom, more preferably hydrogen atom or optionally substituted hydroxyl group, especially preferably hydrogen atom or C_{1-4} alkoxy groups.

In the formulae (I) and (II), L and M represent hydrogen atom, or they may optionally be combined with each other to form a bond. L and M are preferably hydrogen atom.

In the compounds wherein L and M are combined with each other to form a bond, there exist (E) and (Z)-isomers relative to The double bond at the 5-position of the azolidinedione ring.

And, in the compounds wherein L and M respectively represent hydrogen atom, there exist (R)- and (S)-optical isomers due to the asymmetric carbon at the 5-position of the azolidinedione ring. The compounds include these (R)- and (S)-optical isomers and racemic isomers.

Preferable examples of the compounds represented by the formula (I) or (II) includes those in which R is pyridyl, oxazolyl or thiazolyl group optionally having 1 to 3 substituents selected from C_{1-3} alkyl, furyl, thienyl, phenyl and naphthyl; m is 0; n is 0 or 1; X is CH; A is a bond or $-(CH_2)_2-$; R^1 is hydrogen atom; ring E, namely the partial formula:



and R^2 is hydrogen atom or C_{1-4} alkoxy group; and L and M are both hydrogen atom.

Preferable examples of the compound represented by the formula (I) include

(1) the compound represented by the formula (III) such as 5-[4-[2-(3-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione; 5-[4-[2-(4-ethyl-2-pyridyl)ethoxy]-benzyl]-2,4-thiazolidinedione; 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (generic name: pioglitazone); and 5-[4-[2-(6-ethyl-2-pyridyl)-ethoxy]benzyl]-2,4-thiazolidinedione;

(2)-(R)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione; and

(3) 5-[[4-[(3,4-dihydro-6 -hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (generic name: troglitazone/CS-045).

The compound represented by the formula (I) is especially preferably pioglitazone.

The compound represented by the formula (II) is preferably the compound represented by the formula (III) and (R)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione, more preferably pioglitazone.

The pharmacologically acceptable salt of the compound represented by the formula (I) or (II) are exemplified by salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

Preferable examples of salts with inorganic bases include salts with alkali metals such as sodium, potassium, etc., salts with alkaline earth metals such as calcium, magnesium, etc., and salts with aluminum, ammonium, etc.

Preferable examples of salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, etc.

Preferable examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.

Preferable examples of salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.

Preferable examples of salts with basic amino acids include salts with arginine, lysine, ornithine, etc., and preferable examples of salts with acidic amino acids include salts with aspartic acid, glutamic acid, etc.

The pharmacologically acceptable salt of the compound represented by the formula (III) is preferably a salt with an inorganic acid, more preferably a salt with hydrochloric acid. Especially, pioglitazone is preferably used in the form of salt with hydrochloric acid.

The compounds represented by the formula (I) or (II) or a salt-thereof can be produced in accordance with, for example, methods described in JPA S55(1980)-22636(EP-A 8203), JPA S60(1985)-208980(EP-A 155845), JPA S61(1986)-286376(EP-A 208420), JPA S61(1986)-85372(EP-A 177353), JPA S61(1986)-267580(EP-A 193256), JPA H5(1993)-86057(WO 92/18501), JPA H7(1995)-82269 (EP-A 605228), JPA H7(1995)-101945(EP-A 612743), EP-A 643050, EP-A 710659, etc. or methods analogous thereto.

Insulin sensitivity enhancers include 5-[[3,4-dihydro-2-(phenylmethyl)-2H-1-benzopyran-6-yl]methyl]-2,4-thiazolidinedione (generic name: englitazone) or its sodium salt;

5-[[4-[3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl]phenyl]methyl]-2,4-thiazolidinedione (generic name: darglitazone/CP-86325) or its sodium salt;

5-[2-(5-methyl-2-phenyl-4-oxazolylmethyl)benzofuran-5-ylmethyl]-2,4-oxazolidinedione (CP-92768);

5-(2-naphthalenylsulfonyl)-2,4-thiazolidinedione (AY-31637);

4-[(2-naphthalenyl)methyl]-3H-1-1,2,3,5-oxathiadiazol-2-oxide (AY-30711); and

5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]-methyl]-2,4-thiazolidinedione (BRL-49653), etc. in addition to compounds mentioned hereinbefore.

In the present invention, examples of the drug which is used in combination with the above-mentioned insulin sensitivity enhancer include an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor.

α-Glucosidase inhibitors are drugs which inhibit digestive enzymes such as amylase, maltase, α-dextrinase, sucrase, etc. to retard digestion of starch and sugars. Examples of the α-glucosidase inhibitors include acarbose, N-(1,3-dihydroxy-2-propyl)valiolamine (generic name; voglibose), miglitol, etc. with preferance given to voglibose.

Aldose reductase inhibitors are drugs which inhibit the first-stage rate-limiting enzyme in the polyol pathway to prevent or arrest diabetic complications. In the hyperglycemic state of diabetes, the utilization of glucose in the polyol pathway is increased and the excess sorbitol accumulated intracellularly as a consequence acts as a tissue toxin and hence evokes the onset of complications such as diabetic neuropathy, retinopathy, and nephropathy. Examples of the aldose reductase inhibitors include tolurestat; epalrestat; 3,4-dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxazine-4-acetic acid; 2,7-difluoro-spiro(9H-fluorene-9,4'-imidazolidine)-2',5'-dione (generic name: imirestat);

3-[(4-bromo-2-fluorophenyl)methyl]-7-chloro-3,4-dihydro-2,4-dioxo-1(2H)-quinazoline acetic acid (generic name: zenarestat);

6-fluoro-2,3-dihydro-2',5'-dioxo-spiro[4H-1-benzopyran-4,4'-imidazolidine]-2-carboxamide (SNK-860); zopolrestat; sorbinil; and

1-[(3-bromo-2-benzofuranyl)sulfonyl]-2,4-imidazolidinedione (M-16209), etc.

Biguanides are drugs having actions of stimulation of anaerobic glycolysis, increase of the sensitivity to insulin in the peripheral tissues, inhibition of glucose absorption from the intestine, suppression of hepatic gluconeogenesis, and inhibition of fatty acid oxidation. Examples of the biguanides include phenformin, metformin, buformin etc.

Statin compounds are drugs having actions of lowering blood cholesterol levels by inhibiting hydroxymethylglutalyl CoA (HMG-CoA) reductase. Examples of the statin compounds include pravastatin and its sodium salt, simvastatin, lovastatin, atorvastatin, fluvastatin, etc.

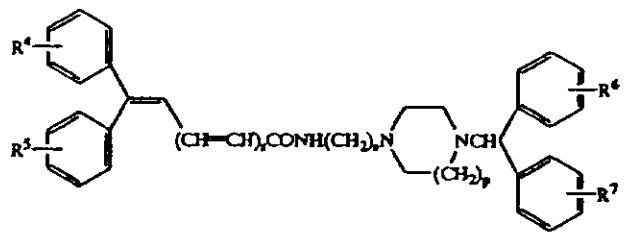
Squalene synthesis inhibitors are drugs having actions of lowering blood cholesterol levels by inhibiting synthesis of squalene. Examples of the squalene synthesis inhibitors include (S)-α-[Bis[2,2-dimethyl-1-oxopropoxy)methoxy] phosphinyl]-3-phenoxybenzenebutanesulfonic acid, mono potassium salt (EMS-188494).

Fibrate compounds are drugs having actions of lowering blood cholesterol levels by inhibiting synthesis and secretion of triglycerides in liver and activating a lipoprotein lipase.

Examples of the fibrate compounds include bezafibrate, beclobrate, binifibrate, ciplofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate, etc.

LDL catabolism enhancers are drugs having actions of lowering blood cholesterol levels by increasing the number of LDL, (low-density lipoprotein) receptors.

Examples of the LDL catabolism enhancers include the compound which is described in JPA H7(1995)-316144 and represented by the formula:



wherein R^4, R^5, R^6 and R^7 are the same or different, and represent hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group; r is 0–2; s is 2–4; p is 1–2; or a salt thereof; specifically N-[2-[4-bis(4-fluorophenyl) methyl-1-piperazinyl]ethyl]-7,7-dipbenyl-2,4,6-heptatrienic acid amide, etc.

The above-mentioned statin compounds, squalene synthesis inhibitors, fibrate compounds and LDL catabolism enhancers can be substituted with other drugs having the property to lower blood cholesterol and triglyceride levels. Examples of these drugs include nicotinic acid derivatives such as nicomol and niceritrol; antioxidants such as probucol; and ion-exchange resins such as colestyramin.

Angiotensin converting enzyme inhibitors are drugs having actions of partially lowering blood glucose levels as well as lowering blood pressure by inhibiting angiotensin converting enzymes. Examples of the angiotensin converting enzyme inhibitors include captopril, enalapril, alacepril, delapril, ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moveltopril, perindopril, quinapril, spirapril,temocapril, trandolapril, etc.

In the present invention, especially preferred is the pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with an α-glucosidase inhibitor. The insulin sensitivity enhancer is especially preferably pioglitazone, and the α-glucosidase inhibitor is especially preferably voglibose.

In the present invention, examples of the drug which is used in combination with the compound represented by the formula (II) or a pharmacologically acceptable salt thereof include an insulin secretion enhancer and/or an insulin preparation.

Insulin secretion enhancers are drugs having the property to promote secretion of insulin from pancreatic β cells. Examples of the insulin secretion enhancers include sulfonylureas (SU). The sulfonylureas (SU) are drugs which promote secretion of insulin from pancreatic β cells by transmitting signals of insulin secretion via SU receptors in the cell membranes. Examples of the SU include tolbutamide; chlorpropamide; tolazamide; acetohexamide; 4-chloro-N-[(1-pyrolidinylamino)carbonyl]-benzenesulfonamide (generic name: glycopyramide) or its ammonium salt; glibenclamide (glyburide); gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; tolcyclamide, etc.

Insulin secretion enhancers include N-[[4-(1-methylethyl) cyclohexyl]carbonyl]-D-phenylalanine (AY-4166); calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl) propionate dihydrate (KAD-1229); and glimepiride (Hoe 490), etc. in addition to compounds mentioned hereinbefore. The insulin secretion enhancer is especially preferably glibenclamide.

Examples of the insulin preparations include animal insulin preparations typically extracted from bovine or porcine pancreas and human insulin preparations synthesized by genetic engineering techniques typically using *Escherichia coli* or yeasts. While insulin preparations are available in a variety of types, e.g. immediate-acting, bimodal-acting, intermediate-acting, and long-acting, these types of preparations can be selectively administered according to the patient's condition.

In the present invention, especially preferred is the pharmaceutical composition which comprises the compound represented by the formula (II) or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer. The compound represented by the formula (II) or a pharmacologically acceptable salt thereof is especially preferably pioglitazone, and the insulin secretion enhancer is especially preferably glibenclamide.

The pharmaceutical composition comprising an insulin sensitivity enhancer in combination with at least one member selected from the group consisting of an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor; and the pharmaceutical composition comprising the compound represented by the formula (II) or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation, both provided in accordance with the present invention, can be respectively put to use by mixing the respective active components either all together or independently with a physiologically acceptable carrier, excipient, binder, diluent, etc. and administering the mixture or mixtures either orally or non-orally as a pharmaceutical composition. When the active components are formulated independently, the respective formulations can be extemporaneously admixed using a diluent or the like and administered or can be administered independently of each other, either concurrently or at staggered times to the same subject.

The dosage form for said pharmaceutical composition includes such oral dosage forms as granules, powders, tablets, capsules, syrups, emulsions, suspensions, etc. and such non-oral dosage forms as injections (e.g. subcutaneous, intravenous, intramuscular and intraperitoneal injections), drip infusions, external application forms (e.g. nasal spray preparations, transdermal preparations, ointments, etc.), and suppositories (e.g. rectal and vaginal suppositories).

These dosage forms can be manufactured by the per se known technique conventionally used in pharmaceutical procedures. The specific manufacturing procedures are as follows.

To manufacture an oral dosage form, an excipient (e.g. lactose, sucrose, starch, mannitol, etc.), a disintegrator (e.g. calcium carbonate, carboxymethylcellulose calcium, etc.), a binder (e.g. α-starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, etc.), and a lubricant (e.g. talc, magnesium stearate, polyethylene glycol 6000, etc.), for instance, are added to the active component or components and the resulting composition is compressed. Where necessary, the compressed product is coated, by the per se known technique, for masking the taste or for enteric dissolution or sustained release. The coating material that can be used includes, for instance, ethylcellulose, hydroxymethylcellulose polyoxyethylene glycol, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, and Eudragit (Rohm & Haas, Germany, methacrylic-acrylic copolymer).

Injections can be manufactured typically by the following procedure. The active component or components are dissolved, suspended or emulsified in an aqueous vehicle (e.g. distilled water, physiological saline, Ringer's solution, etc.) or an oily vehicle (e.g. vegetable oil such as olive oil, sesame oil, cottonseed oil, corn oil, etc. or propylene glycol) together with a dispersant (e.g. Tween 80 (Atlas Powder, U.S.A.), HCO 60 (Nikko Chemicals), polyethylene glycol, carboxymethylcellulose, sodium alginate, etc.), a preservative (e.g. methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, benzyl alcohol, chlorobutanol, phenol, etc.), an isotonizing agent (e.g. sodium chloride, glycerol, sorbitol, glucose, inverted sugar, etc.) and other additives. If desired, a solubilizer (e.g. sodium salicylate, sodium acetate, etc.), a stabilizer (e.g. human serum albumin), a soothing agent (e.g. benzalkonium chloride, procaine hydrochloride, etc.) and other additives can also be added.

A dosage form for external application can be manufactured by processing the active component or components into a solid, semi-solid or liquid composition. To manufacture a solid composition, for instance, the active component or components, either as they are or in admixture with an excipient (e.g. lactose, mannitol, starch, microcrystalline cellulose, sucrose, etc.), a thickener (e.g. natural gums, cellulose derivatives, acrylic polymers, etc.), etc., are processed into powders. The liquid composition can be manufactured in substantially the same manner as the injections mentioned above. The semi-solid composition is preferably provided in a hydrous or oily gel form or an ointment form. These compositions may optionally contain a pH control agent (e.g. carbonic acid, phosphoric acid, citric acid, hydrochloric acid, sodium hydroxide, etc.), and a preservative (e.g. p-hydroxybenzoic acid esters, chlorobutanol, benzalkonium chloride, etc.), among other additives.

Suppositories can be manufactured by processing the active component or components into an oily or aqueous composition, whether solid, semi-solid or liquid. The oleaginous base that can be used includes, for instance, higher fatty acid glycerides [e.g. cacao butter, Witepsols (Dinamit-Nobel), etc.], mnedium-chain fatty acids [e.g. Migriols (Dinamit-Nobel), etc.], vegetable oils (e.g. sesame oil, soybean oil, cotton-seed oil, etc.), etc. The water-soluble base includes, for instance, polyethylene glycols, propylene glycol, etc. The hydrophilic base includes, for instance, natural gums, cellulose derivatives, vinyl polymers, and acrylic polymers, etc.

The pharmaceutical composition of the present invention is low in toxicity and can be safely used in mammals (e.g. humans, mice, rats, rabbits, dogs, cats; bovines, horses, swines, monkeys).

The dosage of the pharmaceutical composition of the present invention may be appropriately determined with reference to the dosages recommended for the respective active components and can be selected appropriately according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of the active components, among other factors. For example, the dosage of the insulin sensitivity enhancer for an adult can be selected from the clinical oral dose range of 0.01 to 10 mg/kg body weight (preferably 0.05 to 10 mg/kg body weight, more preferably 0.05 to 5 mg/kg body weight) or the clinical parenteral dose range of 0.005 to 10 mg/kg body weight (preferably 0.01 to 10 mg/kg body weight, more preferably 0.01 to 1 mg/kg body weight). The other active component or components having different modes of action for use in combination can also be used in dose ranges selected by referring to the respective recommended clinical dose ranges. The preferred frequency of administration is 1 to 3 times a day.

The proportions of the active components in the pharmaceutical composition of the present invention can be appropriately selected according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of active components, among other factors. When, for example, the compound represented by the formula (I) or a pharmacologically acceptable salt thereof (e.g. pioglitazone) which is the insulin sensitivity enhancer and voglibose which is an α-glucosidase inhibitor are to be administered in combination to a human subject, voglibose is used in a proportion of usually about 0.0001 to 0.2 weight parts and preferably about 0.001 to 0.02 weight parts relative to 1 weight part of the compound or a salt thereof. When, for example the compound represented by the formula (II) or a pharmacologically acceptable salt thereof and glibenclamide which is an insulin secretion enhancer are to be administered in combination to a human subject, glibenclamide is used in a proportion of usually about 0.002 to 5 weight parts and preferably about 0.025 to 0.5 weight parts, relative to 1 weight part of the compound or a pharmacologically acceptable salt thereof.

The pharmaceutical composition of the present invention shows a marked synergistic effect compared with administration of either active component alone. For example, compared with cases in which each of these active components was administered to diabetic Wistar fatty rats with genetical obsesity, administration of these active components in combination resulted in marked improvements in both hyperglycemia and reduced glucose tolerance. Thus, the pharmaceutical composition of the present invention lowers blood glucose in diabetics more effectively than it is the case with administration of each component drug alone and, therefore, can be used advantageously for the prophylaxis and treatment of diabetic complications.

Furthermore, since the pharmaceutical composition of the present invention develops sufficient efficacy with reduced doses as compared with the administration of any one of the active components alone, the side effects of the respective components (e.g. gastrointestinal disorders such as diarrhea, etc.) can be reduced.

The following working examples and experimental examples are merely intended to illustrate the present invention in further detail but should by no means be construed as defining the scope of the invention.

The pharmaceutical composition of the present invention can be prepared according to the following formulations.

WORKING EXAMPLE 1

Capsules	
(1) Pioglitazone hydrochloride	30 mg
(2) Voglibose	0.2 mg
(3) Lactose	60 mg
(4) Microcrystalline cellulose	79.8 mg
(5) Magnesium stearate	10 mg
Total	180 mg

The whole amounts of (1), (2), (3) and (4) and half the amount of (5) are mixed well and granulated in the conventional manner. Then, the balance of (5) is added and, after mixing, the whole composition is filled in a gelatin hard capsule shell.

WORKING EXAMPLE 2

Tablets	
(1) Pioglitazone hydrochloride	10 mg
(2) Glibenclamide	1.25 mg
(3) Lactose	86.25 mg
(4) Corn starch	20 mg
(5) Polyethylene glycol	2.5 mg
(6) Hydroxypropylcellulose	4 mg
(7) Carmellose calcium	5.5 mg
(8) Magnesium stearate	0.5 mg
	130 mg (per tablet)

The whole amounts of (1), (2), (3), (4), and (5), ⅗ amounts of (6) and (7), and ½ amount of (8) are mixed well and granulated in the conventional manner. Then, the balances of (6), (7) and (8) are added to the granules, which is mixed well and the whole composition is compressed with a tablet machine. The adult dosage is 3 tablets/day, to be taken in 1 to 3 divided doses.

WORKING EXAMPLE 3

Capsules	
(1) Pioglitazone hydrochloride	10 mg
(2) Epalrestat	50 mg
(3) Lactose	55 mg
(4) Microcrystalline cellulose	55 mg
(5) Magnesium stearate	10 mg
Total	180 mg

The whole amounts of (1), (2), (3) and (4) and ½ amount of (5) are mixed well and granulated in the conventional manner. Then, the balance of (5) is added and the whole composition is filled in gelatin capsule shell. The adult dosage is 3 capsules/day, to be taken in 1 to 3 divided doses.

EXPERIMENTAL EXAMPLE 1

Effect of pioglitazone hydrochloride in combination with α-glucosidase inhibitor in genetically obese and diabetic Wistar fatty rats

Male Wistar fatty rats aged 14–19 weeks were divided into 4 groups of 5–6, and pioglitazone hydrochloride (1 mg/kg body wt./day, p.o.) and/or voglibose (an α-glucosidase inhibitor) (0.31 mg/kg body wt./day; administered by mixing in commercial diet at a rate of 5 ppm) was administered for 14 days. The blood was then collected from the tail vein and the plasma glucose and hemoglobin A_1 were determined by the enzymatic method (Encore Chemical System, Baker) and using a commercial kit (NC-ROPET, Nippon Chemiphar Co.), respectively. The results were expressed in mean ± standard deviation for each group (n=5–6) and analyzed by Dunnett's test, which are shown in Table 1. The 1% level of significance was used.

TABLE 1

Group	Plasma glucose (mg/dl)	Hemoglobin A (%)
Control	345 ± 29	5.7 ± 0.4
Pioglitazone	215 ± 50*	5.2 ± 0.3

TABLE 1-continued

Group	Plasma glucose (mg/dl)	Hemoglobin A (%)
Voglibose	326 ± 46	6.0 ± 0.6
Pioglitazone + voglibose	114 ± 23*	4.5 ± 0.4*

*: P < 0.01 vs. control group

It is apparent from Table 1 that both the blood glucose and hemoglobin A_1 levels were remarkably lowered by combined administration of pioglitazone and voglibose as compared with the administration of either drug alone.

EXPERIMENTAL EXAMPLE 2

Effect of pioglitazone hydrochloride in combination with an insulin secretion enhancer in genetically obese and diabetic Wistar fatty rats Male Wistar fatty rats aged 13–14 weeks were divided into 4 groups of 5, and pioglitazone hydrochloride (3 mg/kg/day, p.o.) and/or glibenclamide (an insulin secretion enhancer) (3 mg/kg/day, p.o.) was administered for 7 days. Following an overnight fast, the oral glucose loading test (2 g glucose/kg/5 ml, p.o.) was carried out. Prior to glucose loading and 120 and 240 minutes after the loading, blood was collected from the tail vein and the plasma glucose was assayed by the enzymatic method (Encore Chemical System, Baker). The results were expressed in mean ± SD for each group (n=5) and analyzed by Dunnett's test, which are shown in Table 2.

TABLE 2

Group	Plasma glucose (mg/dl) 0 min.	120 min.	240 min.
Control	119 ± 9	241 ± 58	137 ± 10
Pioglitazone	102 ± 12	136 ± 17*	102 ± 9*
Glibenclamide	118 ± 12	222 ± 61	106 ± 24*
Pioglitazone + glibenclamide	108 ± 3	86 ± 10*	60 ± 5*

*: P < 0.01 vs. control group

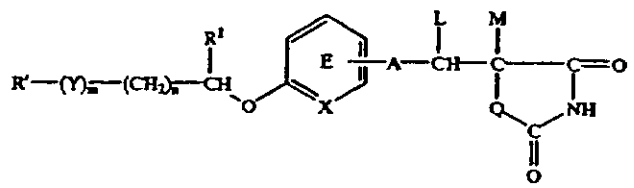
It is apparent from Table 2 that the increase of blood sugar following glucose loading was remarkably inhibited by the combined administration of pioglitazone and glibenclamide as compared with the administration of either drug alone.

The pharmaceutical composition of the present invention shows a potent depressive effect on diabetic hyperglycemia and is useful for prophylaxis and treatment of diabetes. Moreover, this pharmaceutical composition is useful for prophylaxis and treatment of diabetic complications such as diabetic neuropathy, nephropathy, retinopathy, macroangiopathy, and osteopenia. In addition, by appropriately selecting the kinds of component drugs, administration route, dosage, etc. according to clinical status, stable hypoglycemic efficacy in long-term therapy can be expected with an extremely low risk of side effect.

What is claimed is:

1. A method for reducing the amount of respective active components administered to a diabetic patient, which comprises administering to said patient a therapeutically effective amount of a compound represented by the formula:

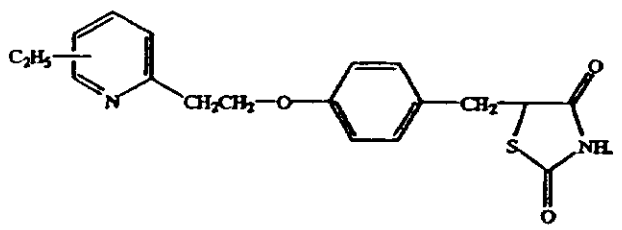
(II)



wherein R' represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR^3— wherein R^3 represents an optionally substituted alkyl group; m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents an oxygen atom or sulfur atom; R^1 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 further substituents, and the substituents may optionally be combined with R^1 to form a ring; L and M respectively represent a hydrogen atom, or L and M may optionally be combined with each other to form a bond; with a proviso that R' does not represent benzopyranyl group when m and n are 0, X represents CH, A represents a bond, Q represents sulfur atom, R^1, L and M represent hydrogen atoms and ring E does not have further substituents; or a pharmacologically acceptable salt thereof, in combination with an insulin secretion enhancer.

2. The method according to claim 1, wherein the compound represented by the formula (II) is the compound represented by the formula:

(III)



3. The method according to claim 1, wherein the compound represented by the formula (II) is pioglitazone or its pharmacologically acceptable salts.

4. The method according to claim 1, wherein the insulin secretion enhancer is glibenclamide.

5. The method according to claim 1, wherein the compound represented by the formula (II) is pioglitazone and the insulin secretion enhancer is glibenclamide.

6. The method according to claim 1, wherein the compound represented by the formula (II) is 5-[[4-[2-methyl-2-pyridylamino)ethoxy]phenyl]methyl-2,4-thiazolidinedione or its pharmacologically acceptable salts.

7. The method according to claim 1, wherein the compound represented by the formula (II) is troglitazone or its pharmacologically acceptable salts.

8. The method according to claim 1, wherein the insulin secretion enhancer is a sulfonylurea.

9. The method according to claim 8, wherein the sulfonylurea is selected from tolbutamide, chlorpropamide, tolazamide, acetohexamide, 4-chloro-N-[(1-pyrolidinylamino)carbonyl]-benzenesulfonamide or its ammonium salt, glibenclamide, gliclazide, 1-butyl-3-metanilylurea, carbutamide, glibonuride, glipizide,

gliquidone, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide and tolcyclamide.

10. The method according to claim 1, wherein R' is an optionally substituted heterocyclic group.

11. The method according to claim 10, wherein R' is selected from the group consisting of 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, 1H-indazol-3-yl, 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-pyridin-2-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-b]pyrazin-2-yl and benzopyranyl; each of which may have 1 to 5 substituents selected from the group consisting of C_{1-15} aliphatic hydrocarbon group; C_{3-12} alicyclic hydrocarbon group; C_{6-14} aryl group; aromatic heterocyclic group selected form the group consisting of furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4,-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, 1,2-benzoisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylidinyl, purinyl, pteridinyl, carbozolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenathridinyl, phenathrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl; non-aromatic heterocyclic group selected from the group consisting of oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidino, piperidino, morpholino and thiomorpholino; halogen atom; nitro group; amino groups which may have one or two substituents selected from C_{1-10} alkyl group; C_{2-10} alkenyl group, C_{2-10} alkynyl group, aromatic group, heterocyclic group or C_{1-10} acyl group; C_{1-13} acyl group which may be substituted by C_{1-13} alkyl group, C_{1-13} alkoxy group, halogen atom, nitro group, hydroxyl group or amino group; hydroxyl group; C_{1-10} alkoxy group; C_{3-10} cycloalkyloxy group; C_{2-10} alkenyloxy group; C_{3-10} cycloalkenyloxy group; C_{7-10} aralkyloxy group; C_{2-13} acyloxy group; C_{6-14} aryloxy group which may be substituted with one or two halogen atoms; thiol group; C_{1-10} alkylthio group; C_{3-10} cycloalkylthio group; C_{2-10} alkenylthio group; C_{3-10} cycloalkenylthio group, C_{7-10} aralkylthio group, C_{2-13} acylthio group; C_{6-14} arylthio group which may be substituted with one or two halogen atoms; carboxyl group; C_{2-5} alkoxycarbonyl group; C_{8-10} aralkyloxycarbonyl group; C_{7-15} aryloxycarbonyl group; amidino group; carbamoyl group; sulfamoyl group; sulfo group; cyano group; azido group and nitroso group.

12. The method according to claim 1, wherein the insulin secretion enhancer is selected from the group consisting of N-[[4-(1-methylethyl)cyclohexyl)carbonyl]-D-phenylalanine; calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl) propionate dihydrate and glimepiride.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,211,205 B1
DATED : April 3, 2001
INVENTOR(S) : Hitoshi Ikeda et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 18, claim 6,
Line 2, change "[2-methyl" to -- [2-(methyl --;
Line 3, change "methyl-2" to -- methyl]-2 --.

Column 19, claim 11,
Line 11, change "[4,5-pyridin" to -- [4,5-b]pyridin --;
Line 12, change "[4,5-b]" to -- [4,5-c] --;
Line 17, change "form" to -- from --;
Line 19, change "1,2,4,-oxadiazolyl" to -- 1,2,4-oxadiazolyl --;
Line 28, change "carbozolyl" to -- carbazolyl --;

Column 20, claim 11,
Line 43, change "group;" to -- group, --;
Line 45, change "C_{1-13}" (both occurrences) to -- C_{1-3} --;
Line 50, change "C_{8-14}" to -- C_{6-14} --.
Line 53, change "," (both occurrences) to -- ; --;
Line 59, change "group and" to -- group; and --.

Column 20, claim 12,
Line 5, after "dihydrate" insert -- ; --.

Signed and Sealed this

Twelfth Day of March, 2002

Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

US006271243B1

(12) **United States Patent**
Ikeda et al.

(10) **Patent No.: US 6,271,243 B1**
(45) **Date of Patent: Aug. 7, 2001**

(54) **PHARMACEUTICAL COMPOSITION**

(75) Inventors: **Hitoshi Ikeda, Higashiosaka; Takashi Sohda, Takatsuki; Hiroyuki Odaka, Kobe, all of (JP)**

(73) Assignee: **Takeda Chemical Industries, Ltd., Osaka (JP)**

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/722,597**

(22) Filed: **Nov. 28, 2000**

Related U.S. Application Data

(62) Division of application No. 09/605,704, filed on Jun. 29, 2000, which is a division of application No. 09/280,710, filed on Mar. 30, 1999, now Pat. No. 6,150,383, which is a division of application No. 09/057,465, filed on Apr. 9, 1998, now Pat. No. 5,965,584, which is a division of application No. 08/667,979, filed on Jun. 19, 1996, now Pat. No. 5,952,356.

(30) **Foreign Application Priority Data**

Jun. 20, 1995 (JP) 7-153500

(51) Int. Cl.[7] C07D 401/02; A61K 31/42; A61K 31/44; A61K 31/425

(52) U.S. Cl. 514/342; 514/340; 514/369; 514/376; 546/269.7; 546/271.4; 548/183; 548/227

(58) Field of Search 548/183.227; 546/269.7, 546/271.4; 514/340, 342, 369.376

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(List continued on next page.)

Primary Examiner—Zinna Northington Davis
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(57) **ABSTRACT**

Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with other antidiabetics differing from the enhancer in the mechanism of action, which shows a potent depressive effect on diabetic hyperglycemia and is useful for prophylaxis and treatment of diabetes.

7 Claims, No Drawings

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PHARMACEUTICAL COMPOSITION

This application is a divisional of application Ser. No. 09/605,704, filed Jun. 29, 2000, now allowed which is a divisional of Ser. No. 09/280,710 filed Mar. 30, 1999, now U.S. Pat. No. 6,150,383 which is a divisional of Ser. No. 09/057,465 filed Apr. 9, 1998, now U.S. Pat. No. 5,965,584, which is a divisional of application Ser. No. 08/667,979, filed Jun. 19, 1996, now U.S. Pat. No. 5,952,356.

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition comprising an insulin sensitivity enhancer in combination with one or more other antidiabetics differing from said enhancer.in the mechanism of action.

BACKGROUND OF THE INVENTION

Recent years, the pathology of diabetes has become more and more understood and, in parallel, drugs specific for the respective pathologic states have been developed. Accordingly a variety of drugs hating new mechanisms of action have appeared one after another.

Insulin sensitivity enhancers are also known as insulin resistance deblockers because they have the action to normalize the impaired insulin receptor function, and are gathering much attention in these years.

Regarding such insulin sensitivity enhancers, a very useful compound such as pioglitazone has been developed [Pujita et al., Diabetes, 32, 804–810, 1983, JP-A, S55 (1980)-22636 (EP-A 8203), JP-A S61(1986)-267580 (EP-A 193256)]. Pioglitazone restores the impaired insulin receptor function to normalize the uneven distribution of glucose transporters in cells, the cardinal enzyme systems associated with glycometabolism, such as glucokinase, and enzyme systems associated with lipidmetabolism, such as lipoprotein lipase. As the results, insulin resistance are deblocked to improve glucose tolerance, and lower the plasma concentrations of neutral lipids and free fatty acids. Since these actions of pioglitazone are comparatively gradual and thle risk of side effect in long-term administration is also low, this compound is useful for obese patients who are presumed to be highly insulin-resistant.

Also, insulin sensitivity enhancers such as CS-045, thazolidinedione derivatives and substituted thiazolidinedione derivatives are reported to be used in combination with insulin [JP-A H4(1992)-66579, JP-A H4(1992)-69383, JP-A H5(1993)-202042]. However, the pharmaceutical composition having a specific combination of the present invention is unknown.

Diabetes is a chronic disease with diverse pathologic manifestations and is accompanied by lipidmetabolism disorders and circulatory disorders as well as glycometabolism disorders. As the results, diabetes tends to progress entailing various complications in many cases. Therefore, it is necessary to select the drug of choice for the prevailing disease state in each individual case. However, this selection is often difficult in clinical settings because single use of each individual drug can not bring sufficient effects in some disease states and there are various problems such as side effect which is caused by an increased dose or a long-term administration.

SUMMARY OF THE INVENTION

In view of the above state of the art the inventors of the present invention did much research to develop antidiabetics

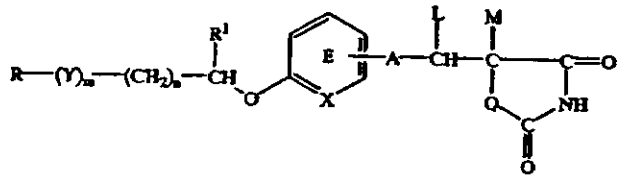
which would not virtually cause adverse reactions even on long-term administration and could be effective for a large cohort of the diabetic population. As a consequence, they discovered that the above object can be accomplished by using an insulin sensitivity enhancer, such as the drug described above, in combination with other antidiabetics differing from said enhancer in the mechanism of action, and accordingly have perfected the present invention.

The present invention, therefore, relates to:

1) Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with at least one member of the group consisting of an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor;

2) Pharmaceutical composition according to 1), wherein the insulin sensitivity enhancer is a:compound represented by the formula:

(I)



wherein R represents an optionally substituted hydrocarbon or heterocyclic group; Y representsa group represented by —CO—, —CH(OH)— or —NR^3— (wherein R^3 represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R^1 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 substituents, and the substituents may optionally be combined with R^1 to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; or a pharmacologically acceptable salt thereof;

3) Pharmaceutical composition according to 2), wherein the compound represented by the formula (I) is pioglitazone;

4) Pharmaceutical composition according to 1), which comprises an insulin sensitivity enhancer in combination with an α-glucosidase inhibitor;

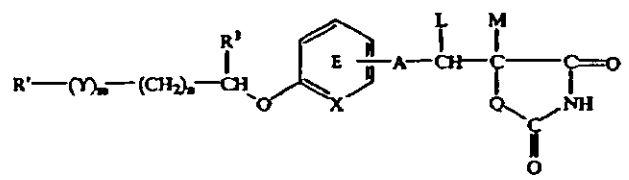
5) Pharmaceutical composition according to 4), wherein the α-glucosidase inhibitor is voglibose;

6) Pharmaceutical composition according to 4), wherein the insulin sensitivity enhancer is pioglitazone and the α-glucosidase inhibitor is voglibose;

7) Pharmaceutical composition according to 1), which is for prophylaxis or treatment of diabetes;

8) Pharmaceutical composition which comprises a compound represented by the formula:

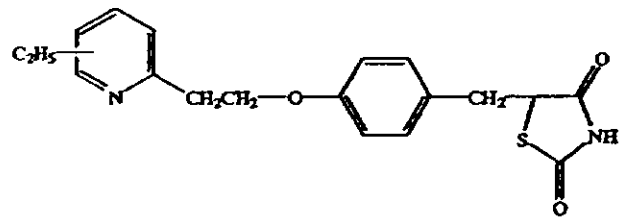
(II)



wherein R' represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR^3— (wherein R^3 represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R^1 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 substituents, and the substituents may optionally be combined with R^1 to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; with a proviso that R' does not represent benzopyranyl group when m and n are 0, X represents CH, A represents a bond, Q represents sulfur atom, R^1, L and M represent hydrogen atom and ring E does not have further substituents; or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation;

9) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is the compound represented by the formula:

(III)



10) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is pioglitazone;

11) Pharmaceutical composition according to 8), wherein the insulin secretion enhancer is glibenclamide;

12) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is pioglitazone and the insulin secretion enhancer is glibenclamide;

13) Pharmaceutical composition according to 8), which is for prophylaxis or treatment of diabetes.

DETAILED DESCRIPTION OF THE INVENTION

The term "insulin sensitivity enhancer" as used in this specification means any and all drug substances that restore the impaired insulin receptor function to deblock insulin resistance and consequently enhance insulin sensitivity. As examples of the insulin sensitivity enhancer, the compound represented by the formula (I) or a pharmacologically acceptable salt thereof can be mentioned.

In the formula (I), as the hydrocarbon group in the optionally substituted hydrocarbon group represented by R, mention is made of aliphatic i. hydrocarbon groups, alicyclic hydrocarbon groups, alicyclic-aliphatic hydrocarbon groups, aromatic aliphatic hydrocarbon groups and aromatic hydrocarbon groups. Number of carbon atoms in these hydrocarbon groups is preferably 1 to 14.

The aliphatic hydrocarbon groups are preferably those having 1 to 8 carbon atoms. As the aliphatic hydrocarbon groups, mention is made of C_{1-8} saturated aliphatic hydrocarbon groups (e.g. alkyl group) as exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, hexyl, isohexyl, heptyl and octyl, and C_{2-8} unsaturated aliphatic hydrocarbon groups (e.g. alkenyl group, alkadienyl group, alkynyl group, alkadiynyl group) as exemplified by vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptynyland 1-octynyl.

The alicyclic hydrocarbon groups are preferably those having 3 to 7 carbon atoms. As the alicyclic hydrocarbon groups, mention is made of C_{3-7} saturated alicyclic hydrocarbon groups (e.g. cycloalkyl group) as exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and C_{5-7} unsaturated alicyclic hydrocarbon groups (e.g. cycloalkenyl group, cycloalkadienyl group) as exemplified by 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl and 2,4-cycloheptadienyl.

As the alicyclic-aliphatic hydrocarbon groups, mention is made of, among those formed by combination of the above-mentioned alicyclic hydrocarbon groups with aliphatic hydrocarbon groups (e.g. cycloalkyl-alkyl group, cycloalkenyl-alkyl group), ones having 4 to 9 carbon atoms as exemplified by cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylinethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl and cycloheptylethyl.

The aromatic aliphatic hydrocarbon groups are preferably those having 7 to 13 carbon atoms (e.g. aralkcyl group). As the aromatic aliphatic hydrocarbon groups, mention is made of C_{7-9} phenylal-kyl as exemplified by benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and 1-phenylpropyl, and C_{11-13} naphthylalkyl as exemplified by α-naphthylmethyl, α-naphthylethyl, β-naphthylmethyl and β-naphthylethyl.

As the aromatic hydrocarbon groups, mention is made of, ones having 6 to 14 carbon atoms as exemplified by phenyl, naphthyl (α-naphtyl, β-naphthyl).

In the formula (I), as the heterocyclic group in the optionally substituted heterocyclic group represented by R, mention is made of, for example, 5- to 7-membered heterocyclic groups containing, as a ring component atom, 1 to 4 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom, and a condensed ring group. As the condensed ring, mention is made of, for example, these 5- to 7-membered heterocyclic groups condensed with 6-membered ring containing one or two nitrogen atoms, benzene ring or 5-membered ring containing one sulfur atom.

Examples of these heterocyclic groups include 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl,

5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, 1H-indazol-3-yl, 1H-pyrrolo [2,3-b]pyrazin-2-yl, 1Hpyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 1H-imidazo[4,5-b]pyrazin-2-yl and benzopyranyl. Among them, pyridyl, oxazolyl or thiazolyl group is preferable.

In the formula (I), the hydrocarbon group and heterocyclic group represented by R may optionally have 1 to 5, preferably 1 to 3 substituents at any substitutable positions. Examples of such substituents include aliphatic hydrocarbon group, alicyclic hydrocarbon group, aryl group, aromatic heterocyclic group, non-aromatic heterocyclic group, halogen atom, nitro group, optionally substituted amino group, optionally substituted acyl group, optionally substituted hydroxyl group, optionally substituted thiol group, optionally esterified carboxyl group, amidino group, carbamoyl group, sulfamoyl group, sulfo group, cyano group, azido group and nitroso group.

Examples of the aliphatic hydrocarbon groups include C_{1-15} straight-chain or branched aliphatic hydrocarbon groups as exemplified by alkyl group, alkcenyl group, and alkynyl group.

Preferable examples of the alksyl group include C_{1-10} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, hexyl, pentyl, octyl., nonyl and decyl.

Preferable examples of the alkenyl group include C_{2-10} alicenyl groups such as vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl.

Preferable examples of the alkynyl group include C_{2-10} alkynyl groups such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As the alicyclic hydrocarbon group, mention is made of C_{3-12} saturated or unsaturated alicyclic hydrocarbon groups as exemplified by cycloalkyl group, cycloalkenyl group and cycloalkadienyl group.

Preferable examples of cycloalkyl group include C_{3-10} cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo [2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1] nonyl and bicyclo[4.3.1]decyl.

Preferable examples of the cycloalkenyl group include C_{3-10} cycloalkenyl groups such as 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl and 3-cyclohexen-1-yl.

Preferable examples of the cycloalkadienyl group include C_{4-10} cycloalkadienyl groups such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl and 2,5-cyclohexadien-1-yl.

Preferable examples of the aryl group include C_{6-14} aryl groups such as phenyl, naphthyl (1-naphthyl, 2-naphthyl), anthryl, phenanthryl and acenaphthylenyl.

Preferable examples of the aromatic heterocyclic group include aromatic monocyclic heterocyclic groups such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolylt 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl; and aromatic condensed heterocyclic groups such as benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, 1,2-benzoisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylidinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenathridinyl, phenathrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, uiidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a] pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo [4,3-b]pyridazinyl.

Preferable examples of the non-aromatic heterocyclic group include oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, mprpholinyl, thiomorpholinyl, piperazinyl, pyrrolidino, piperidino, morpholino and thiomorpholino.

Examples of the halogen atom include fluorine, chlorine, bromine and iodine.

As the substituted amino group in the optionally substituted amino group, mention is made of, N-monosubstituted amino group and N,N-disubstituted amino group. Examples of the substituted amino groups include amino groups having one or two substituents selected from C_{1-10} alkyl group, C_{210} alkenyl group, C_{2-10} alkynyl group, aromatic group, heterocyclic group and C_{1-10} acyl group (e.g. methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclobexylamino, phenylamino, N-methyl-N-phenyl-amino, acetylamino, propionylamino, benzoylamino and nicotinoylamino).

As the acyl group, mention is made of C_{1-13} acyl groups such as C_{1-10} alkcanoyl group, C_{3-10} alkenoyl group, C_{4-10} cycloalkapoyl group, C_{4-10} cycloalkenoyl group and C_{6-12} aromatic carbonyl group.

Preferable examples of the C_{1-10} alkanoyl group include formyl acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl and octanoyl. Preferable examples of the C_{3-10} alkenoyl group include acryloyl, methacryloyl, crotonoyl and isocrotonoyl. Preferable examples of C_{4-10} cycloalkanoyl group include cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl and cycloheptanecarbonyl. Preferable examples of C_{4-10} cycloalkenoyl group include 2-cyclohexenecarbonyl. Preferable examples of C_{6-12} aromatic carbonyl group include benzoyl, naphthoyl and nicotinoyl.

As the substituent in the substituted acyl group, mention is made of, for example, C_{1-3} alkyl group, C_{1-3} alkoxy group, halogen atom (e.g. chlorine, fluorine, bromine, etc.), nitro group, hydroxyl group and amino group.

As the substituted hydroxyl group in the optionally substituted hydroxyl group, mention is made of, for example, alkoxy group, cycloalkyloxy group, alkenyloxy group, cycloalkcenyloxy group, aralkyloxy group, acyloxy group and aryloxy group.

Preferable examples of the alkoxy group include C_{1-10} alkoxy groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, t.-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy and nonyloxy. Preferable examples of the cycloalkyloxy group include C_{3-10} cycloalkyloxy groups such as cyclobutoxy, cyclopentyloxy and cyclohexyloxy. Preferable examples of the alkenyloxy group include C_{2-10} alkenyloxy groups such as allyloxy, crotyloxy, 2-pentenyloxy and 3-hexenyloxy. Preferable examples of the cycloalkenyloxy group include C_{3-10} cycloalkenyloxy groups such as 2-cyclopentenyloxy and 2-cyclohexenyloxy. Preferable examples of the aralkyloxy group include C_{7-10} aryloxy groups such as phenyl-C_{1-4}alkyloxy (e.g. benzyloxy and phenethyloxy). Preferable examples of the acyloxy group include C_{2-13} acyloxy group, more preferably C_{2-4} alkanoyloxy groups (e.g. acetyloxy, propionyloxy, butyryloxy and isobutyryloxy). Preferable examples of the aryloxy group include C_{6-14} aryloxy groups such as phenoxy and naphthyloxy. The aryloxy group may optionally have one or two substituents such as halogen atom (e.g. chlorine, fluorine, bromine). Examples of the substituted aryloxy group include 4-chlorophenoxy.

As the substituted thiol group in the optionally substituted thiol group, mention is made of, alkylthio group, cycloalkylthio group, alkenylthio group, cycloalkenylthio group, aralkylthio group, acylthio group and arylthio group.

Preferable examples of the alkylthio group include C_{1-10} alkylthio groups such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec.-butylthio, t.-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio and nonylthio. Preferable examples of the cycloalkylthio group include C_{3-10} cycloalkylthio groups such as cyclobutylthio, cyclopentylthio and cyclohexylthio. Preferable examples of the alkenylthio group include C_{2-10} alkenylthio groups such as allylthio, crotylthio, 2-pentenylthio and 3-hetenylthio. Preferable examples of the cycloalkenylthio group include C_{3-10} cycloalkenylthia groups such as 2-cyclopentenylthio and 2-cyclohexenylthio. Preferable examples of the aralkylthio include C_{7-10} aralkylthio groups such as phenyl-C_{1-4}alkylthio (e.g. benzylthio and phenethylthio). Preferable examples of the acylthio group include C_{2-13} acylthio group, more preferably C_{2-4} alkanoylthio groups (e.g. acetylthio, propionylthio, butyrylthio and isobutyrylthio).

Preferable examples of the arylthio group include C_{6-14} arylthio groups such as phenylthio and naphthylthio. The arylthio group may optionally have one or two substituents such as halogen atom (e.g. chlorine, fluorine, bromine). Examples of the substituted arylthio group include 4-chlorophenylthio.

As the optionally esterified carboxyl group, mention is made of, for example, alkoxycarbonyl group, aralkyloxycarbonyl group and aryloxycarbonyl group.

Preferable examples of the alkoxycarbonyl group include C_{2-5} alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and butoxycarbonyl. Preferable examples of the aralkyloxycarbonyl group include C_{8-10} aralcyloxycarbonyl groups such as benzyloxycarbonyl. Preferable examples of the aryloxycarbonyl group include C_{7-15} aryloxycarbonyl groups such as phenoxycarbonyl and p-tolyloxycarbonyl.

Among the substituents on the hydrocarbon group and heterocyclic group represented by R, C_{1-10} alkyl groups, aromatic heterocyclic groups and C_{6-10} aryl groups are preferable, and C_{1-3} alkyl, furyl, thienyl, phenyl and naphthyl are especially preferable.

In the formula (I), substituents on the hydrocarbon group and heterocyclic group which are represented by R, may, when they are alicyclic hydrocarbon group, aryl group, aromatic heterocyclic group or non-aromatic heterocyclic group, have one or more, preferably 1 to 3, of suitable substituents respectively. Examples of these substituents include C_{1-6} alkyl groups, C_{2-6} alkenyl groups, C_{2-6} alkynyl groups, C_{3-7} cycloalkyl groups, C_{6-14} aryl groups, aromatic heterocyclic groups (e.g. thienyl, furyl, pyridyl, oxazolyl and thiazolyl), non-aromatic heterocyclic groups (e.g. tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolidino and piperazino), C_{7-9} aralkyl groups, amino group, N-mono-C_{1-4} alkylamino groups, N,N-di-C_{1-4} alkylamino groups, C_{2-8} acylamino groups (e.g. acetylamino, propionylamino and benzoylamino), amidino group, C_{2-8} acyl group (e.g. C_{2-8} alkcanoyl groups), carbamoyl group, N-mono-C_{1-4} alkcyl carbamoyl groups, N,N-di-C_{1-4} alkyl carbamoyl groups, sulfamoyl group, N-mono-C_{1-4} alkyl sulfamoyl groups, N,N-di-C_{1-4} alkyl sulfamoyl groups, carboxyl group, C_{2-8} alkoxycarbonyl groups, hydroxyl group, C_{1-4} alkoxy groups, C_{2-5} alkenyloxy groups, C_{3-7} cycloalkyloxy groups, C_{7-9} aralkyloxy groups, C_{6-14} aryloxy groups, mercapto group, C_{1-4} alkylthio groups, C_{7-9} aralkylthio groups C_{6-14} arylthio groups, sulfo group, cyano group, azido group, nitro group, nitroso group and halogen atom.

In the formula (I), R is preferably an optionally substituted heterocyclic group. R is more preferably pyridyl, oxazolyl or thiazolyl-group which is optionally substituted by 1 to 3 substituents selected from C_{1-3} alkyl group, furyl group, thienyl group, phenyl group and naphthyl group.

R' in the formula (II) has the same definition as R except that R' does not represent benzopyranyl group when m and n are O; X represents CH; A represents a bond; Q represents sulfur atom; R^1, L and M represent hydrogen atom; and ring E does not have further substituents.

In the formulae (I) and (II), Y represents —CO—, —CH(OH)— or —NR^3— (wherein R^3 represents an optionally substituted alkyl group), preferably —CH(OH)— or —NR^3—. As the alkyl group in the optionally substituted alkyl group represented by R^3, mention is made of, for example, C_{1-4} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl and t.-butyl. Examples of the substituents include halogen (e.g., fluorine, chlorine, bromine and iodine), C_{1-4} alkoxy groups (e.g. methoxy, ethoxy, propoxy, butoxy, isobutoxy, sec.-butoxy and t.-butoxy), hydroxyl group, nitro group and C_{1-4} acyl groups (e.g. formyl, acetyl and propionyl).

The symbol m is 0 or 1, preferably 0.

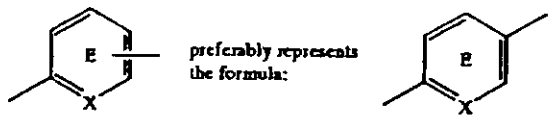
The symbol n is 0, 1 or 2, preferably 0 or 1.

X represents CH or N, preferably CH.

In the formulae (I) and (II), A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group. The aliphatic hydrocarbon group may be straight-chain or branched, and saturated or unsaturated. Specific examples of the aliphatic hydrocarbon group include saturated ones [e.g. —CH_2—, —$CH(CH_3)$—, —$(CH_2)_2$—, —$CH(C_2H_5)$—, —$(CH_2)_3$—, —$(C_2)_4$—, —$(CH_2)_5$—, —$(C_2)_6$— and —$(CH_2)_7$—] and unsaturated ones [e.g. —CH=CH—, —$C(CH_3)$=CH—, —CH=CH—CH_2—, —$C(C_2H_5)$=CH—, —CH_2—CH=CH—CH_2—, —CH_2—CH_2—CH=CH—CH_2—, —CH=CH—CH=CH—CH_2— and —CH=CH—CH=CH—CH=CH—CH_2—. A is preferably a bond or C_{1-4} divalent aliphatic hydrocarbon groups, the aliphatic hydrocarbon groups preferably being saturated. A is more preferably a bond or —$(CH_2)_2$—.

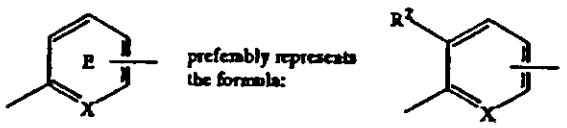
As the alkyl group represented by R^1, substantially the same one as the alkyl group in the above-mentioned R^3. R^1 is preferably hydrogen atom.

In the formulae (I) and (II), the partial formula:



Ring E has 1 to 4 substituents at any substitutable positions. Examples of such substituents include alkyl group, optionally substituted hydroxyl group, halogen atom, optionally substituted acyl group and optionally substituted amino group. These substituents have substantially the same meaning as those described as substituents of the hydrocarbon group and heterocyclic group represented by R.

Ring E, namely the partial formula:



wherein R^2 represents hydrogen atom, an alkyl group, an optionally substituted hydroxyl group, a halogen atom, an optionally substituted acyl group, nitro group or an optionally substituted amino group.

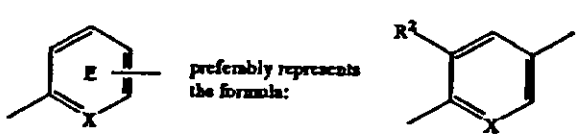
As the alkyl group, optionally substituted hydroxyl group, halogen atom, optionally substituted acyl group and optionally substituted amino group represented by R^2, mention is made of those described as substituents of the hydrocarbon group and heterocyclic group represented by R. R^2 is preferably hydrogen atom, optionally substituted hydroxyl group or halogen atom, more preferably hydrogen atom or optionally substituted hydroxyl group, especially preferably hydrogen atom or C_{1-4} alkoxy groups.

In the formulae (I) and (II), L and M represent hydrogen atom, or they may optionally be combined with each other to form a bond. L and M are preferably hydrogen atom.

In the compounds wherein L and M are combined with each other to form a bond, there exist (E)- and (Z)-isomers relative to the double bond at the 5-position of the azolidinedione ring.

And, in the compounds wherein L and M respectively represent hydrogen atom, there exist (R)- and (S)-optical isomers due to the asymmetric carbon at the 5-position of the azolidinedione ring. The compounds include these (R)- and (S)-optical isomers and racemic isomers.

Preferable examples of the compounds represented by the formula (I) or (II) includes those inwhich R is pyridyl, oxazolyl or thiazolyl group optionally having 1 to 3 substituents selected from C_{1-3} alkyl, furyl, thienyl, phenyl and naphthyl; m is 0; n is 0 or 1; X is CH; A is a bond or $—(CH_2)_2—$; R^1 is hydrogen atom; ring E, namely the partial formula:



and R^2 is hydrogen atom or C_{1-4} alkoxy group; and L and M are both hydrogen atom.

Preferable examples of the compound represented by the formula (I) include

(1) the compound represented by the formula (III) such as 5-[4-[2-(3-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione; 5-[4-[2-(4-ethyl-2-pyridyl)ethoxy]-benzyl]-2,4-thiazolidinedione; 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (generic name: pioglitazone); and 5-[4-[2-(6-ethyl-2-pyridyl)-ethoxy]benzyl]-2,4-thiazolidinedione;

(2) (R)-(+)-5-[3-[4-[2-(2furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione; and

(3) 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)Tnethoxylphenyl]methyl]-2,4-thiazolidinedione (generic namne: troglitazone/CS-045).

The compound represented by the formula (I) is especially preferably pioglitazone.

The compound represented by the formula (II) is preferably the compound represented by the formula (III) and (R)-(+)-5-[3-[4-(2-(2-furyl)-5-niethyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione, more preferably pioglitazone.

The pharmacologically acceptable salt of the compound represented by the formula (I) or (II) are exemplified by salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

Preferable examples of salts with inorganic bases include salts with alkali metals such as sodium, potassium, etc., salts with alkaline earth metals such as calcium magnesium, etc., and salts with aluminum, ammonium, etc.

Preferable examples of salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, etc.

Preferable examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.

Preferable examples of salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric. acid, oxalic acid, tartaric acid, maleic acid, citric acid, succimic acid, malic acid, methanesulfonic acid. benzenesulfonic acid, p-tohuenesulfonic acid, etc.

Preferable examples of salts with basic amino acids include salts with arginine, lysine, ornithine, etc., and preferable examples of salts with acidic amino acids include salts with aspartic acid, glutamic acid, etc.

The pharmacologically acceptable salt of the compound represented by the formula (III) is preferably a salt with an inorganic acid, more preferably a salt with hydrochloric acid. Especially, pioglitazone is preferably used in the form of salt with hydrochloric acid.

The compounds represented by the formula (I) or (II) or a saltthereof can be produced in accordance with, for example, methods described in JPA S55(1980)-22636(EP-A 8203), JPA S60(1985)-208980(EP-A 155845), JPA S61 (1986)-286376(EP-A 208420), JPA S61(1986)-85372(EP-A 177353), JPA S61(1986)-267580(EP-A 193256), JPA H5(1993)-86057(WO 92/18501), JPA H7(1995)-82269 (EP-A 605228), JPA H7(1995)-101945(EP-A 612743), EP-A. 643050, EP-A 710659, etc. or methods analogous thereto.

Insulin sensitivity enhancers include 5-[[3,4-dihydro-2-(phenylmethyl)-2H-1-benzopyran-6-yl]methyl]-2,4-thiazolidinedione (generic name: englitazone) or its sodium salt;

5-[[4-[3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl] phenyl]methyl]-2,4-thiazolidinedione (generic name: darglitazone/CP-86325) or its sodium salt;

5-[2-(5-methyl-2-phenyl-4-oxazolylmethyl)benzofuran-5-ylmethyl]-2,4-oxazolidinedione (CP-92768);

5-(2-naphthalenylsulfonyl)-2,4-thiazolidinedione (AY-31637);

4-[(2-naphthalenyl)methyl]-3H-1,2,3,5-oxathiadiazol-2-oxide (AY-30711); and

5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]-methyl]-2,4-thiazolinedione (BRL-49653), etc. in addition to compounds mentioned hereinbefore.

In the present invention, examples of the drug which is used in combination with the above-mentioned insulin sensitivity enhancer include an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor.

α-Glucosidase inhibitors are drugs which inhibit digestive enzymes suchas amylase, maltase, α-dextrinase, sucrase, etc. to retard digestion of starch and sugars. Examples of the α-glucosidase inhibitors include acarbose, N-(1,3-dihydroxy-2-propyl)valiolamine (generic name; voglibose), miglitol, etc. with preferance given to voglibose.

Aldose reductase inhibitors are drugs which inhibit the first-stage rate-limitting enzyme in the polyol pathway to prevent or arrest diabetic complications. In the hyperglycemic state of diabetes, the utilization of glucose in the polyol pathway is increased and the excess sorbitol accumulated intracellularly as a consequence acts as a tissue toxin and hence evokes the onset of complications such as diabetic neuropathy, retinopathy, and nephropathy. Examples of the aldose reductase inhibitors include tolurestat; epalrestat; 3,4-dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxazine-4-acetic acid; 2,7-difluoro-spiro(9H-fluorene-9,4'-imidazolidine)-2',5'-dione (generic name: imirestat);

3-[(4-bromo-2-fluorophenyl)methyl]-7-chloro-3,4-dihydro-2,4-dioxo-1(2H)-quinazoline acetic acid (generic name: zenarestat);

6-fluoro-2,3-dihydro-2',5'-dioxo-spiro[4H-1-benzopyran-4,4'-imidazolidine]-2-carboxamide (SNK-860);

zopolrestat; sorbinil; and

1-[(3-bromo-2-benzofuranyl)sulfonyl]-2,4-imidazolidinedione (M-16209), etc.

Biguanides are drugs having actions of stimulation of anaerobic glycolysis, increase of the sensitivity to insulin in the peripheral tissues, inhibition of glucose absorption from the intestine, suppression of hepatic gluconeogenesis, and inhibition of fatty acid oxidation. Examples of the biguanides include phenformin, metformin, buformin etc.

Statin compounds are drugs having actions of lowering blood cholesterol levels by inhibiting hydroxymethylglutalyl CoA (HMG-CoA) reductase. Examples of the statin compounds include pravastatin and its sodium salt, simvastatin, lovastatin, atorvastatin, fluvastatin, etc.

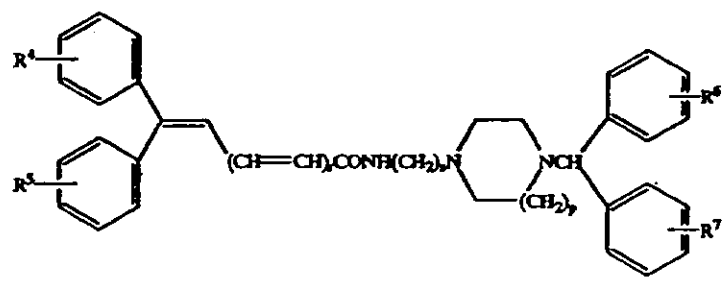
Squalene synthesis inhibitors are drugs having actions of lowering blood cholesterol levels by inhibiting synthesis of squalene. Examples of the squalene synthesis inhibitors include (S)-α-[Bis[2,2-dimethyl-1-oxopropoxy)methoxy] phosphinyl]-3-phenoxybenzenebutanesulfonic acid, mono potassium salt (BMS-188494).

Fibrate compounds are drugs having actions of lowering blood cholesterol levels by inhibiting synthesis and secretion of triglycerides in liver and activating a lipoprotein lipase.

Examples of the fibrate compounds include bezafibrate, beclobrate, binifibrate, ciplofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, siufibrate, theofibrate, etc.

LDL catabolism enhancers are drugs having actions of lowering blood cholesterol levels by increasing the number of LDL (low-density lipoprotein) receptors.

Examples of the LDL catabolism enhancers include the compound which is described in JPA H7(1995)-316144 and represented by the formula:



wherein R^4, R^5, R^6 and R^7 are the same or different, and represent hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group; r is 0–2; s is 2–4; p is 1–2; or a salt thereof; specifically N-[2-[4-bis(4-fluorophenyl) methyl-1-piperazinyl]ethyl]-7,7-diphenyl-2,4,6-heptatrienic acid amide, etc.

The above-mentioned statin compounds, squalene synthesis inhibitors, fibrate compounds and LDL catabolism enhancers can be substituted with;other drugs having the property to lower blood cholesterol and triglyceride levels. Examples of these drugs include nicotinic acid derivatives such as nicomol and niceritrol; antioxidants such as probucol; and ion-exchange resins such as colestyramin.

Angiotensin converting enzyme inhibitors are drugs having actions of partially lowering blood glucose levels as well as lowering blood pressure by inhibiting angiotensin converting enzymes. Examples of the angiotensin converting enzyme inhibitors include captopril, enalapril, alacepril, delapril, ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moveltopril, perindopril, quinapril, spirapril, temocapril, trandolapril, etc.

In the present invention, especially preferred is the pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with an α-glucosidase inhibitor. The insulin sensitivity enhancer is especially preferably pioglitazone, and the α-glucosidase inhibitor is especially preferably voglibose.

In the present invention, examples of the drug which is used in combination with the compound represented by the formula (II) or a pharmacologically acceptable salt thereof include an insulin secretion enhancer and/or an insulin preparation.

Insulin secretion enhancers are drugs having the property to promote secretion of insulin from pancreatic β cells. Examples of the insulin secretion enhancers include sulfonylureas (SU). The sulfonylureas (SU) are drugs which

promote secretion of insulin from pancreatic β cells by transmitting signals of insulin secretion via SU receptors in the cell membranes. Examples of the SU includetolbutamide; chlorpropamide; tolazamide; acetohexanmide; 4-chloro-N-[(1-pyrolidinylamino)carbonyl]-benzenesulfonamide (generic name: glycopyramide) or its ammonium salt; glibenclamide (glyburide); gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; tolcyclamide, etc.

Insulin secretion enhancers include N-[[4-(1-methylethyl) cyclohexyl)carbonyl]-D-phenylalanine (AY-4166); calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl) propionate dihydrate KAD-1229); and glimepiride (Hoe 490), etc. in addition to compounds mentioned hereinbefore. The insulin secretion enhancer is especially preferably glibenclamide.

Examples of the insulin preparations include animal insulin preparations typically extracted from bovine or porcine pancreas and human insulin. preparations synthesized by genetic engineering techniques typically using *Escherichia coli* or yeasts. While insulin preparations are available in a variety of types, e.g. immediate-acting, bimodal-acting, intermediate-acting, and long-acting, these types of preparations can be selectively administered according to the patient's condition.

In the present invention, especially preferred is the pharmaceutical composition which comprises the compound represented by the formula (II) or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer. The compound represented by the formula (II) or a pharmacologically acceptable salt thereof is especially preferably pioglitazone, and the insulin secretion enhancer is especially preferably glibenclamide.

The pharmaceutical composition comprising an insulin sensitivity enhancer in combination with at least one member selected from the group consisting of an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor; and the pharmaceutical composition comprising the compound represented by the formula (II) or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation, both provided in accordance with the present invention, can be respectively put to use by mixing the respective active components either all together or independently with a physiologically acceptable carrier, excipient, binder, diluent, etc. and administering the mixture or mixtures either orally or non-orally as a pharmaceutical composition. When the active components are formulated independently, the respective formulations can be extemporaneously admixed using a diluent or the like and administered or can be administered independently of each other, either concurrently or at staggered times to the same subject.

The dosage form for said pharmaceutical composition includes such oral dosage forms as granules, powders, tablets, capsules, syrups, emulsions, suspensions, etc. and such non-oral dosage forms as injections (e.g. subcutaneous, intravenous, intramuscular and intraperitoneal injections), drip infusions, external application forms (e.g. nasal spray preparations, transdermal preparations, ointments, etc.), and suppositories (e.g. rectal and vaginal suppositories).

These dosage forms can be manufactured by the per se known technique conventionally used in pharmaceutical procedures. The specific manufacturing procedures are as follows.

To manufacture an oral dosage form, an excipient (e.g. lactose, sucrose, starch, mannitol, etc.), a disintegrator (e.g. calcium carbonate, carboxymethylcellulose calcium, etc.), a binder (e.g. α-starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, etc.), and a lubricant (e.g. talc, magnesium stearate, polyethylene glycol 6000, etc.), for instance, are added to the active component or components and the resulting composition is compressed. Where necessary, the compressed product is coated, by the per se known technique, for masking the taste or for enteric dissolution or sustained release. The coating material that can be used includes, for instance, ethylcellulose, hydroxymethylcellulose, polyoxyethylene glycol, cellulose acetate phthalate, hydroxypropylmethylcellulose phtlialate, and Eudragit (Rohm & Haas, Germany, methacrylic-acrylic copolymer).

Injections can be manufactured typically by the following procedure. The active component or components are dissolved, suspended or emulsified in an aqueous vehicle (e.g. distilled water, physiological it saline, Ringer's solution, etc.) or an oily vehicle (e.g. vegetable oil such as olive oil, sesame oil; cottonseed oil, corn oil, etc. or propylene glycol) together with a dispersant (e.g. Tween 80 (Atlas Powder, U.S.A.), HCO 60 (Nikko Chemicals), polyethylene glycol, carboxymethylcellulose, sodium alginate, etc.), a preservative (e.g. methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, benzyl alcohol, chlorobutanol, phenol, etc.), an.isotonizing agent (e.g. sodium chloride, glycerol, sorbitol, glucose, inverted sugar, etc.) and other additives. If desired, a solubilizer (e.g. sodium salicylate, sodium acetate, etc.), a stabilizer (e.g. human serum albumin), a soothing agent (e.g. benzalkonium chloride, procaine hydrochloride, etc.) and other additives can also be added.

A dosage form for external application can be manufactured by processing the active component or components into a solid, semi-solid or liquid composition. To manufacture a solid composition, for instance, the active component or components, either as they are or in admixture with an excipient (e.g. lactose, mannitol, starch, microcrystalline cellulose, sucrose, etc.), a thickener (e.g. natural gums, cellulose derivatives, acrylic polymers, etc.), etc., are processed into powders. The liquid composition can be manufactured in substantially the same manner as the injections mentioned above. The semi-solid composition is preferably provided in a hydrous or oily gel form or an ointment form. These compositions-may optionally contain a pH control agent (e.g. carbonic acid, phosphoric acid, citric acid, hydrochloric acid, sodium hydroxide, etc.), and a preservative (e.g. p-hydroxybenzoic acid esters, chlorobutanol, benzalkonium chloride, etc.), among other additives.

Suppositories can be manufactured by.processing the active component or components into an oily or aqueous composition, whether solid, semi-solid or liquid. The oleaginous base that can be used includes, for instance, higher fatty acid glycerides [e.g. cacao butter, Witepsols (Dinamit—Nobel), etc.], medium-chain fatty acids [e.g. Migriols (Dinamit-Nobel), etc.], vegetable oils (e.g. sesame oil, soybean oil, cottonseed oil, etc.), etc. The water-soluble base includes, for instance, polyethylene glycols, propylene glycol,. etc. The hydrophilic base includes, for instance, natural gums, cellulose derivatives, vinyl polymers, and acrylic polymers, etc.

The pharmaceutical composition of the present invention is low in toxicity and can be safely used in mammals (e.g. humans, mice, rats, rabbits, dogs, cats, bovines, horses, swines, monkeys).

The dosage of the pharmaceutical composition of the present invention may be appropriately determined with

reference to the dosages recommended for the respective active components and can be selected appropriately according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of the active components, among other factors. For example, the dosage of the insulin sensitivity enhancer for an adult can be selected from the clinical oral dose range of 0.01 to 10 mg/kg body weight (preferably 0.05 to 10 mg/kg body weight, more preferably 0.05 to 5 mg/kg body weight) or the clinical parenteral dose range of 0.005 to 10 mg/kg body weight (preferably 0.01 to 10 mg/kg body weight, more preferably 0.01 to 1 mg/kg body weight). The other active component or components having different modes of action for use in combination can also be used in dose ranges selected by referring to the respective recommended clinical dose ranges. The preferred frequency of administration is 1 to 3 times a day.

The proportions of the active components in the pharmaceutical composition of the present invention can be appropriately selected according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of active components, among other factors. When, for example, the compound represented by the formula (I) or a pharmacologically acceptable salt thereof (e.g. pioglitazone) which is the insulin sensitivity enhancer and voglibose which is an α-glucosidase inhibitor are to be administered in combination to a human subject, voglibose is used in a proportion of usually about 0.0001 to 0.2 weight parts and preferably about 0.001 to 0.02 weight parts relative to 1 weight part of the compound or a salt thereof. When, for example, the compound represented by the formula (II) or a pharmacologically acceptable salt thereof and glibenclamide which is an insulin secretion enhancer are to be administered in combination to a human subject, glibenclamide is used in a proportion of usually about 0.002 to 5 weight parts and preferably about 0.025 to 0.5 weight parts, relative to 1 weightpart of the compound or a pharmacologically acceptable salt thereof.

The pharmaceutical composition of thepresent invention shows a marked synergistic effect compared with administration of either active component alone. For example, compared with cases in which each of these active components was administered to diabetic Wistar fatty rats with genetical obesity, administration of these active components in combination resulted in marked improvements in both hyperglycemia and reduced glucose tolerance. Thus, the pharmaceutical composition of the present invention lowers blood glucose in diabetics more effectively than it is the case with administration of each component drug alone and, therefore, can be used advantageously for the prophylaxis and treatment of diabetic complications.

Furthermore, since the pharmaceutical composition of the present invention develops sufficient efficacy with reduced doses as compared with the administration of any one of the active components alone, the side effects of the respective components (e.g. gastrointestinal disorders such as diarrhea, etc.) can be reduced.

The following working examples and experimental examples are merely intended to illustrate the present invention in further detail but should by no means be construed as defining the scope of theinvention.

The pharmaceutical composition of the present invention can be prepared according to the following formulations.

WORKING EXAMPLE 1

Capsules	
(1) Pioglitazone hydrochloride	30 mg
(2) Voglibose	0.2 mg
(3) Lactose	60 mg
(4) Microcrystalline cellulose	79.8 mg
(5) Magnesium stearate	10 mg
Total	180 mg

The whole amounts of (1), (2), (3) and (4) and half the amount of (5) are mixed well and granulated in the conventional manner. Then, the balance of (5) is added and, after mixing, the whole composition is filled in a gelatin hard capsule shell.

WORKING EXAMPLE 2

Tablets	
(1) Pioglitazone hydrochloride	10 mg
(2) Glibenclamide	1.25 mg
(3) Lactose	86.25 mg
(4) Corn starch	20 mg
(5) Polyethylene glycol	2.5 mg
(6) Hydroxypropylcellulose	4 mg
(7) Carmellose calcium	5.5 mg
(8) Magnesium stearate	0.5 mg
	130 mg (per tablet)

The whole amounts of (1), (2), (3), (4), and (5), ⅗ amounts of (6) and (7), and ½ amount of (8) are mixed well and granulated in the conventional manner. Then, the balances of (6), (7) and (8) are added to the granules, which is mixed well and the whole composition is compressed with a tablet machine. The adult dosage is 3 tablets/day, to be taken in 1 to 3 divided doses.

WORKING EXAMPLE 3

Capsules	
(1) Pioglitazone hydrochloride	10 mg
(2) Epalrestat	50 mg
(3) Lactose	55 mg
(4) Microcrystalline cellulose	55 mg
(5) Magnesium stearate	10 mg
Total	180 mg

The whole amounts of (1), (2), (3) and (4) and ½ amount of (5) are mixed well and granulated in the conventional manner. Then, the balance of (5) is added and the whole composition is filled in gelatin capsule* shell. The adult dosage is 3 capsules/day, to be taken in 1 to 3 divided doses.

EXPERIMENTAL EXAMPLE 1

Effect of pioglitazone hydrochloride in combination with α-glucosidase inhibitor in genetically obese and diabetic Wistar fatty rats

Male Wistar fatty rats aged 14–19 weeks were divided into 4 groups of 5–6, and pioglitazone hydrochloride (1

mg/kg body wt./day, p.o.) and/or voglibose (an Ct-glucosidase inhibitor) (0.31 mg/kg body wt./day; administered by mixing in commercial diet at a rate of 5 ppm) was administered for 14 days. The blood was then collected from the tail vein and the plasma glucose and hemoglobin A_1 were determined by the enzymatic method (Encore Chemical System, Baker) and using a commercial kit (NC-ROPET, Nippon Chemiphar Co.), respectively. The results were expressed in mean ±standard deviation for each group (n=5–6) and analyzed by Dunnett's test, which are shown in Table 1. The 1% level of significance was used.

TABLE 1

Group	Plasma glucose (mg/dl)	Hemoglobin A_1 (%)
Control	345 ± 29	5.7 ± 0.4
Pioglitazone	215 ± 50*	5.2 ± 0.3
Voglibose	326 ± 46	6.0 ± 0.6
Pioglitazone + voglibose	114 ± 23*	4.5 ± 0.4*

*: P < 0.01 vs. control group

It is apparent from Table 1 that both the blood glucose and hemoglobin A_1 levels were remarkably lowered by combined administration of pioglitazone and voglibose as compared with the administration of either drug alone.

EXPERIMENTAL EXAMPLE 2

Effect of pioglitazone hydrochloride in combination with an insulin secretion enhancer in genetically obese and diabetic Wistar fatty rats Male Wistar fatty rats aged 13–14 weeks were divided into 4 groups of 5, and pioglitazone hydrochloride (3 mg/kg/day, p.o.) and/or glibenclamide (an insulin secretion enhancer) (3 mg/kg/day, p.o.) was administered for 7 days. Following an overnight fast, the oral glucose loading test (2 g glucose/kg/5 ml, p.o.) was carried out. Prior to glucose loading and 120 and 240 minutes after the loading, blood was collected from the tail vein and the plasma glucose was assayed by the enzymatic method (Encore Chemical System, Baker). The results were expressed in mean±SD for each group (n=5) and analyzed by Dunnett's test, which are shown in Table 2.

TABLE 2

Group	Plasma glucose (mg/dl) 0 min.	120 min.	240 min.
Control	119 ± 9	241 ± 58	137 ± 10
Pioglitazone	102 ± 12	136 ± 17*	102 ± 9*
Glibenclamide	118 ± 12	222 ± 61	106 ± 24*
Pioglitazone + glibenclamide	108 ± 3	86 ± 10*	60 ± 5*

*: P < 0.01 vs. control group

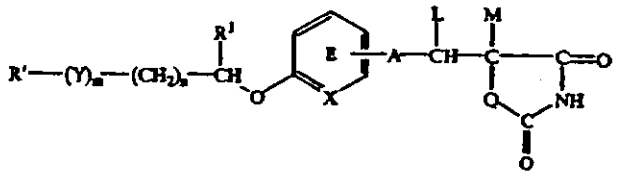
It is apparent from Table 2 that the increase of blood sugar following glucose loading was remarkably inhibited by the combined administration of pioglitazone and glibenclamide as comparedwith the administration of either drug alone.

The pharmaceutical composition of the present invention shows a potent depressive-effect on diabetic hyperglycemia and is useful for prophylaxis and treatment of diabetes. Moreover, this pharmaceutical e composition is useful for prophylaxis and treatment of diabetic complications such as diabetic neuropathy, nephropathy, retinopathy, macroangiopathy, and osteopenia. In addition, by appropriately selecting the kinds of component drugs, administration route, dosage, etc. according to clinical status, stable hypoglycemic efficacy in long-term therapy can be expected with an extremely low risk of side effect.

What is claimed is:

1. A method for reducing the side effects of active components administered to a diabetic patient, which comprises administering to said patient a therapeutically effective amount of a compound represented by the formula:

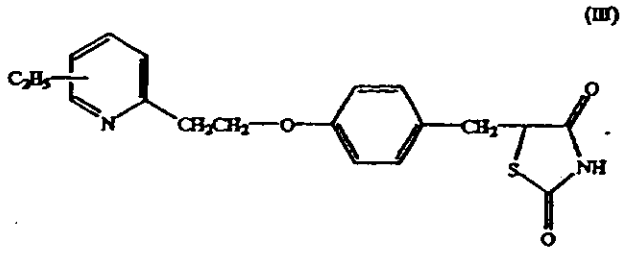
(II)



wherein R' represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR^3— wherein R^3 represents an optionally substituted alkyl group; m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents an oxygen atom or sulfur atom; R^2 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 further substituents, and the substituents may optionally be combined with R^2 to form a ring; L and M respectively represent a hydrogen atom, or L and M may optionally be combined with each other to form a bond; with a proviso that R' does not represent benzopyranyl group when m and n are 0, X represents CH, A represents a bond, Q represents sulfur atom, R^2, L and M represent hydrogen atoms and ring E does not have further substituents; or a pharmacologically acceptable salt thereof, in combination with an insulin preparation as said active components.

2. The method according to claim 1, wherein the compound represented by the formula (II) is the compound represented by the formula:

(III)



3. The method according to claim 1, wherein the compound represented by the formula (II) is pioglitazone or its pharmacologically acceptable salts.

4. The method according to claim 1, wherein the insulin preparation is a human insulin preparation.

5. The method according to claim 1, wherein the compound represented by the formula (II) is 5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]methyl-2,4-thiazolidinedione or its pharmacologically acceptable salts.

6. The method according to claim 1, wherein R' is an optionally substituted heterocyclic group.

7. The method according to claim 6, wherein R' is selected from the group consisting of 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl,

5-oxazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, 1H-indazol-3-yl, 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1 H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 1H-imidazo[4,5-b] pyrazin-2-yl and benzopyranyl; each of which may have 1 to 5 substituents selected from the group consisting of C_{1-15} aliphatic hydrocarbon group; C_{3-12} alicyclic hydrocarbon group; C_{6-14} aryl group; aromatic heterocyclic group selected from the group consisting of furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4,-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, 1,2-benzoisothiazolyl, 1H1-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylidinyl, purinyl, pteridinyl, carbozolyl, α-carbolinyl, β-carbolinyl, y-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenathridinyl, phenathrolinyl, indolizinyl, pyrrolo[2-b]pyridazinyl, pyrazolo[5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b] pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4triazolo[4,3-a] pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl; non-aromatic heterocyclic group selected from the group consisting of oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidino, piperidino, morpholino and thiomorpholino; halogen atom; nitro group; amino groups which may have one or two substituents selected from C_{1-10} alkyl group, C_{2-10} alkenyl group, C_{2-10} alkynyl group, aromatic group, heterocyclic group or C_{1-10} acyl group; C_{1-13} acyl group which may be substituted by C_{1-3} alkyl group, C_{1-3} alkoxy group, halogen atom, nitro group, hydroxyl group or amino group; hydroxyl group; C_{1-10} alkoxy group; C_{3-10} cycloalkyloxy group; C_{2-10} alkenyloxy group; C3-10 cycloalkenyloxy group; C_{7-10} aralkyloxy group; C_{2-13} acyloxy group; C_{6-14} aryloxy group which may be substituted with one or two halogen atoms; thiol group; C_{1-10} alkylthio group; C_{3-10} cycloalkylthio group; C_{2-10} alkenylthio group; C_{3-10} cycloalkenylthio group, C_{7-10} aralkylthio group, C_{2-13} acylthio group; C_{6-14} arylthio group which may be substituted with one or two halogen atoms; carboxyl group; C_{2-5} alkoxycarbonyl group; C_{8-10} aralkyloxycarbonyl group; C_{7-15} aryloxycarbonyl group; amidino group; carbamoyl group; sulfamoyl group; sulfo group; cyano group; azido group and nitroso group.

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US006303640B1

(12) **United States Patent**
Ikeda et al.

(10) **Patent No.: US 6,303,640 B1**
(45) **Date of Patent: Oct. 16, 2001**

(54) **PHARMACEUTICAL COMPOSITION**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 51 days.

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(52) **U.S. Cl.** 514/342; 514/340; 514/369; 514/376; 546/269.7; 546/271.4; 548/183; 548/227

(58) **Field of Search** 546/269.7, 271.4; 548/183.227; 514/340, 342, 369.376

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(57) **ABSTRACT**

Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with other antidiabetics differing from the enhancer in the mechanism of action, which shows a potent depressive effect on diabetic hyperglycemia and is useful for prophylaxis and treatment of diabetes.

12 Claims, No Drawings

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PHARMACEUTICAL COMPOSITION

BACKGROUND OF THE INVENTION

This application is a divisional of application Ser. No. 09/280,710, filed Mar. 30, 1999, now U.S. Pat. No. 6,100,383 which is a divisional of Ser. No. 09/057,465, filed Apr.9, 1998, now U.S. Pat. No. 5,965,584, which is a divisional of application Ser. No. 08/667,979, filed Jun. 19, 1996, now U.S. Pat. No. 5,952,356.

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition comprising an insulin sensitivity enhancer in combination with one or more other antidiabetics differing from said enhancer in the mechanism of action.

Recent years, the pathology of diabetes has become more and more understood and, in parallel, drugs specific for the respective pathologic states have been developed. Accordingly a variety of drugs having new mechanisms of action have appeared one after another.

Insulin sensitivity enhancers are also known as insulin resistance deblockers because they have the action to normalize the impaired insulin receptor function, and are gathering much attention in these years.

Regarding such insulin sensitivity enhancers, a very useful compound such as pioglitazone has been developed [Fujita et al., Diabetes, 32, 804–810, 1983, JP-A S55(1980)-22636 (EP-A 8203), JP-A S61(1986)-267580 (EP-A 193256)]. Pioglitazone restores the impaired insulin receptor function to normalize the uneven distribution of glucose transporters in cells, the cardinal enzyme systems associated with glycometabolism, such as glucokinase, and enzyme systems associated with lipidmetabolism, such as lipoprotein lipase. As the results, insulin resistance are deblocked to improve glucose tolerance, and lower the plasma concentrations of neutral lipids and free fatty acids. Since these actions of pioglitazone are comparatively gradual and the risk of side effect in long-term administration is also low, this compound is useful for obese patients who are presumed to be highly insulin-resistant.

Also, insulin sensitivity enhancers such as CS-405, thiazolidinedione derivatives and substituted thiazolidinedione derivatives are reported to be used in combination with insulin [JP-A H4(1992)-66579, JP-A H4(1992)-69383, JP-A H5(1993)-202042]. However, the pharmaceutical composition having a specific combination of the present invention is unknown.

Diabetes is a chronic disease with diverse pathologic manifestations and is accompanied by lipidmetabolism disorders and circulatory disorders as well as glycometabolism disorders. As the results, diabetes tends to progress entailing various complications in many cases. Therefore, it is necessary to select the drug of choice for the prevailing disease state in each individual case. However, this selection is often difficult in clinical settings because single use of each individual drug can not bring sufficient effects in some disease states and there are various problems such as side effect which is caused by an increased dose or a long-term administration.

SUMMARY OF THE INVENTION

In view of the above state of the art, the inventors of the present invention did much research to develop antidiabetics which would not virtually cause adverse reactions even on long-term administration and could be effective for a large

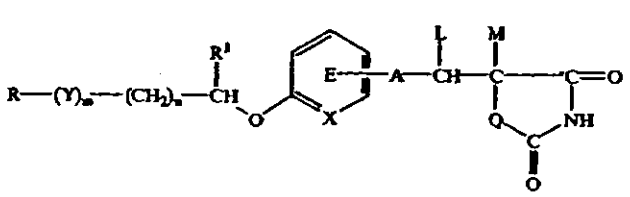
cohort of the diabetic population. As a consequence, they discovered that the above object can be accomplished by using an insulin sensitivity enhancer, such as the drug described above, in combination with other antidiabetics differing from said enhancer in the mechanism of action, and accordingly have perfected the present invention.

The present invention, therefore, relates to:

1) Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with at least one member of the group consisting of α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor;

2) Pharmaceutical composition according to 1), wherein the insulin sensitivity enhancer is a compound represented by the formula:

(I)



wherein R represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR^3— (wherein R^3 represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R^1 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 substituents, and the substituents may optionally be combined with R^1 to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; or a pharmacologically acceptable salt thereof;

3) Pharmaceutical composition according to 2), wherein the compound represented by the formula (I) is pioglitazone;

4) Pharmaceutical composition according to 1), which comprises an insulin sensitivity enhancer in combination with an (α-glucosidase inhibitor;

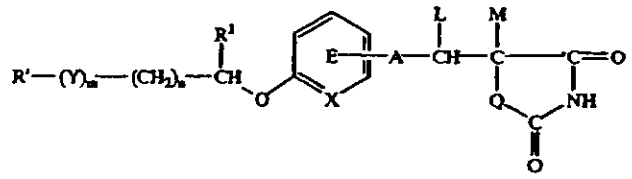
5) Pharmaceutical composition according to 4), wherein the α-glucosidase inhibitor is voglibose;

6) Pharmaceutical composition according to 4), wherein the insulin sensitivity enhancer is pioglitazone and the α-glucosidase inhibitor is voglibose;

7) Pharmaceutical composition according to 1), which is for prophylaxis or treatment of diabetes;

8) Pharmaceutical composition which comprises a compound represented by the formula:

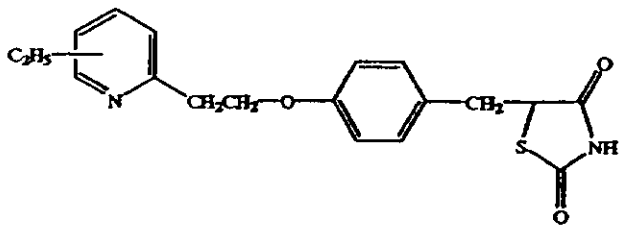
(II)



wherein R' represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR^3— (wherein R^3 represents an optionally substituted alkyl group); m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents oxygen atom or sulfur atom; R^1 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 substituents, and the substituents may optionally be combined with R^1 to form a ring; L and M respectively represent hydrogen atom, or L and M may optionally be combined with each other to form a bond; with a proviso that R' does not represent benzopyranyl group when m and n are 0, X represents CH, A represents a bond, Q represents sulfur atom, R^1, L and M represent hydrogen atom and ring E does not have further substituents; or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation;

9) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is the compound represented by the formula:

(III)



10) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is pioglitazone;

11) Pharmaceutical composition according to 8), wherein the insulin secretion enhancer is glibenclamide;

12) Pharmaceutical composition according to 8), wherein the compound represented by the formula (II) is pioglitazone and the insulin secretion enhancer is glibenclamide;

13) Pharmaceutical composition according to 8), which is for prophylaxis or treatment of diabetes.

DETAILED DESCRIPTION OF THE INVENTION

The term "insulin sensitivity enhancer" as used in this specification means any and all drug substances that restore the impaired insulin receptor function to deblock insulin resistance and consequently enhance insulin sensitivity. As examples of the insulin sensitivity enhancer, the compound represented by the formula (I) or a pharmacologically acceptable salt thereof can be mentioned.

In the formula (I), as the hydrocarbon group in the optionally substituted hydrocarbon group represented by R, mention is made of aliphatic hydrocarbon groups, alicyclic hydrocarbon groups, alicyclic-aliphatic hydrocarbon groups, aromatic aliphatic hydrocarbon groups and aromatic hydrocarbon groups. Number of carbon atoms in these hydrocarbon groups is preferably 1 to 14.

The aliphatic hydrocarbon groups are preferably those having 1 to 8 carbon atoms. As the aliphatic hydrocarbon groups, mention is made of C_{1-8} saturated aliphatic hydrocarbon groups (e.g. alkyl group) as exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, hexyl, isohexyl, heptyl and octyl, and C_{2-8} unsaturated aliphatic hydrocarbon groups (e.g. alkenyl group, alkadienyl group, alkynyl group, alkadiynyl group) as exemplified by vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptynyl and 1-octynyl.

The alicyclic hydrocarbon groups are preferably those having 3 to 7 carbon atoms. As the alicyclic hydrocarbon groups, mention is made of C_{3-7} saturated alicyclic hydrocarbon groups (e.g. cycloalkyl group) as exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and C_{5-7} unsaturated alicyclic hydrocarbon groups (e.g. cycloalkenyl group, cycloalkadienyl group) as exemplified by 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl and 2,4-cycloheptadienyl.

As the alicyclic-aliphatic hydrocarbon groups, mention is made of, among those formed by combination of the above-mentioned alicyclic hydrocarbon groups with aliphatic hydrocarbon groups (e.g. cycloalkyl-alkyl group, cycloalkenyl-alkyl group), ones having 4 to 9 carbon atoms as exemplified by cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl and cycloheptylethyl.

The aromatic aliphatic hydrocarbon groups are preferably those having 7 to 13 carbon atoms (e.g. aralkyl group). As the aromatic aliphatic hydrocarbon groups, mention is made of C_{7-9} phenylalkyl as exemplified by benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and 1-phenylpropyl, and C_{11-13} naphthylalkyl as exemplified by α-naphthylmethyl, α-naphthylethyl, β-naphthylmethyl and β-naphthylethyl.

As the aromatic hydrocarbon groups, mention is made of, ones having 6 to 14 carbon atoms as exemplified by phenyl, naphthyl (α-naphtyl, β-naphthyl).

In the formula (I), as the heterocyclic group in the optionally substituted heterocyclic group represented by R, mention is made of, for example, 5- to 7-membered heterocyclic groups containing, as a ring component atom, 1 to 4 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom, and a condensed ring group. As the condensed ring, mention is made of, for example, these 5- to 7-membered heterocyclic groups condensed with 6-membered ring containing one or two nitrogen atoms, benzene ring or 5-membered ring containing one sulfur atom.

Examples of these heterocyclic groups include 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl,

5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, 1H-indazol-3-yl, 1H-pyrrolo [2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 1H-imidazo[4,5-b]pyrazin-2-yl and benzopyranyl. Among them, pyridyl, oxazolyl or thiazolyl group is preferable.

In the formula (I), the hydrocarbon group and heterocyclic group represented by R may optionally have 1 to 5, preferably 1 to 3 substituents at any substitutable positions. Examples of such substituents include aliphatic hydrocarbon group, alicyclic hydrocarbon group, aryl group, aromatic heterocyclic group, non-aromatic heterocyclic group, halogen atom, nitro group, optionally substituted amino group, optionally substituted acyl group, optionally substituted hydroxyl group, optionally substituted thiol group, optionally esterified carboxyl group, amidino group, carbamoyl group, sulfamoyl group, sulfo group, cyano group, azido group and nitroso group.

Examples of the aliphatic hydrocarbon groups include C_{1-15} straight-chain or branched aliphatic hydrocarbon groups as exemplified by alkyl group, alkenyl group, and alkynyl group.

Preferable examples of the alkyl group include C_{1-10} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, t.-butyl, pentyl, isopentyl, neopentyl, t.-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, hexyl, pentyl, octyl, nonyl and decyl.

Preferable examples of the alkenyl group include C_{2-10} alkenyl groups such as vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl.

Preferable examples of the alkynyl group include C_{2-10} alkynyl groups such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As the alicyclic hydrocarbon group, mention is made of C_{3-12} saturated or unsaturated alicyclic hydrocarbon groups as exemplified by cycloalkyl group, cycloalkenyl group and cycloalkadienyl group.

Preferable examples of cycloalkenyl group include C_{3-10} cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo [2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1] nonyl and bicyclo[4.3.1]decyl.

Preferable examples of the cycloalkenyl group include C_{3-10} cycloalkenyl groups such as 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl and 3-cyclohexen-1-yl.

Preferable examples of the cycloalkadienyl group include C_{4-10} cycloalkadienyl groups such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl and 2,5-cyclohexadien-1-yl.

Preferable examples of the aryl group include C_{6-14} aryl groups such as phenyl, naphthyl (1-naphthyl, 2-naphthyl), anthryl, phenanthryl and acenaphthylenyl.

Preferable examples of the aromatic heterocyclic group include aromatic monocyclic heterocyclic groups such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl; and aromatic condensed heterocyclic groups such as benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, 1,2-benzoisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylidinyl, purinyl, pteridinyl, carbazolyl, αcarbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenathridinyl, phenathrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a] pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo [4,3-b]pyridazinyl.

Preferable examples of the non-aromatic heterocyclic group include oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidino, piperidino, morpholino and thiomorpholino.

Examples of the halogen atom include fluorine, chlorine, bromine and iodine.

As the substituted amino group in the optionally substituted amino group, mention is made of, N-monosubstituted amino group and N,N-disubstituted amino group. Examples of the substituted amino groups include amino groups having one or two substituents selected from C_{1-10} alkyl group, C_{2-10} alkenyl group, C_{2-10} alkynyl group, aromatic group, heterocyclic group and C_{1-10} acyl group (e.g. methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclohexylamino, phenylamino, N-methyl-N-phenyl-amino, acetylamino, propionylamino, benzoylamino and nicotinoylamino).

As the acyl group, mention is made of C_{1-13} acyl groups such as C_{1-10} alkanoyl group, C_{3-10} alkenoyl group, C_{4-10} cycloalkanoyl group, C_{4-10} cycloalkenoyl group and C_{6-12} aromatic carbonyl group.

Preferable examples of the C_{1-10} alkanoyl group include formyl acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl and octanoyl. Preferable examples of the C_{3-10} alkenoyl group include acryloyl, methacryloyl, crotonoyl and isocrotonoyl. Preferable examples of C_{4-10} cycloalkanoyl group include cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl and cycloheptanecarbonyl. Preferable examples of C_{4-10} cycloalkenoyl group include 2-cyclohexenecarbonyl. Preferable examples of C_{6-12} aromatic carbonyl group include benzoyl, naphthoyl and nicotinoyl.

As the substituent in the substituted acyl group, mention is made of, for example, C_{1-3} alkyl group, C_{1-3} alkoxy group, halogen atom (e.g. chlorine, fluorine, bromine, etc.), nitro group, hydroxyl group and amino group.

As the substituted hydroxyl group in the optionally substituted hydroxyl group, mention is made of, for example, alkoxy group, cycloalkyloxy group, alkenyloxy group, cycloalkenyloxy group, aralkyloxy group, acyloxy group and aryloxy group.

Preferable examples of the alkoxy group include C_{1-10} alkoxy groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, t.-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy and nonyloxy. Preferable examples of the cycloalkyloxy group include C_{3-10} cycloalkyloxy groups such as cyclobutoxy, cyclopentyloxy and cyclohexyloxy. Preferable examples of the alkenyloxy group include C_{2-10} alkenyloxy groups such as allyloxy, crotyloxy, 2-pentenyloxy and 3-hexenyloxy. Preferable examples of the cycloalkenyloxy group include C_{3-10} cycloalkenyloxy groups such as 2-cyclopentenyloxy and 2-cyclohexenyloxy. Preferable examples of the aralkyloxy group include C_{7-10} aryloxy groups such as phenyl-C_{1-4}alkyloxy (e.g. benzyloxy and phenethyloxy). Preferable examples of the acyloxy group include C_{2-13} acyloxy group, more preferably C_{2-4} alkanoyloxy groups (e.g. acetyloxy, propionyloxy, butyryloxy and isobutyryloxy). Preferable examples of the aryloxy group include C_{6-14} aryloxy groups such as phenoxy and naphthyloxy. The aryloxy group may optionally have one or two substituents such as halogen atom (e.g. chlorine, fluorine, bromine). Examples of the substituted aryloxy group include 4-chlorophenoxy.

As the substituted thiol group in the optionally substituted thiol group, mention is made of, alkylthio group, cycloalkylthio group, alkenylthio group, cycloalkenylthio group, aralkylthio group, acylthio group and arylthio group.

Preferable examples of the alkylthio group include C_{1-10} alkylthio groups such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec.-butylthio, t.-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio and nonylthio. Preferable examples of the cycloalkylthio group include C_{3-10} cycloalkylthio groups such as cyclobutylthio, cyclopentylthio and cyclohexylthio. Preferable examples of the alkenylthio group include C_{2-10} alkenylthio groups such as allylthio, crotylthio, 2-pentenylthio and 3-hexenylthio. Preferable examples of the cycloalkenylthio group include C_{3-10} cycloalkenylthio groups such as 2-cyclopentenylthio and 2-cyclohexenylthio. Preferable examples of the aralkylthio include C_{7-10} aralkylthio groups such as phenyl-C_{1-4}alkylthio (e.g. benzylthio and phenethylthio). Preferable examples of the acylthio group include C_{2-13} acylthio group, more preferably C_{2-4} alkanoylthio groups (e.g. acetylthio, propionylthio, butyrylthio and isobutyrylthio).

Preferable examples of the arylthio group include C_{6-14} arylthio groups such as phenylthio and naphthylthio. The arylthio group may optionally have one or two substituents such as halogen atom (e.g. chlorine, fluorine, bromine). Examples of the substituted arylthio group include 4-chlorophenylthio.

As the optionally esterified carboxyl group, mention is made of, for example, alkoxycarbonyl group, aralkyloxycarbonyl group and aryloxycarbonyl group.

Preferable examples of the alkoxycarbonyl group include C_{2-5} alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and butoxycarbonyl. Preferable examples of the. aralkyloxycarbonyl group include C_{8-10} aralkyloxycarbonyl groups such as benzyloxycarbonyl. Preferable examples of the aryloxycarbonyl group include C_{7-15} aryloxycarbonyl groups such as phenoxycarbonyl and p-tolyloxyrarbonyl.

Among the substituents on the hydrocarbon group and heterocyclic group represented by R, C_{1-10} alkyl groups, aromatic heterocyclic groups and C_{6-14} aryl groups are preferable, and C_{1-3} alkyl, furyl, thienyl, phenyl and naphthyl are especially preferable.

In the formula (I), substituents on the hydrocarbon group and heterocyclic group which are represented by R, may, when they are alicyclic hydrocarbon group, aryl group, aromatic heterocyclic group or non-aromatic heterocyclic group, have one or more, preferably 1 to 3, of suitable substituents respectively. Examples of these substituents include C_{1-6} alkyl groups, C_{2-6} alkenyl groups, C_{2-6} alkynyl groups, C_{3-7} cycloalkyl groups, C_{6-14} aryl groups, aromatic heterocyclic groups (e.g. thienyl, furyl, pyridyl, oxazolyl and thiazolyl), non-aromatic heterocyclic groups (e.g. tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolidino and piperazino), C_{7-9} aralkyl groups, amino group, N-mono-C_{1-4} alkylamino groups, N,N-di-C_{1-4} alkylamino groups, C_{2-8} acylamino groups (e.g., acetylamino, propionylamino and benzoylamino), amidino group, C_{2-8} acyl group (e.g. C_{2-8} alkanoyl groups), carbamoyl group, N-mono-C_{1-4} alkyl carbamoyl groups, N,N-di-C_{1-4} alkyl carbamoyl groups, sulfamoyl group, N-mono-C_{1-4} alkyl sulfamoyl groups, N,N-di-C_{1-4} alkyl sulfamoyl groups, carboxyl group, C_{2-8} alkoxycarbonyl groups, hydroxyl group, C_{1-4} alkoxy groups, C_{2-5} alkenyloxy groups, C_{3-7} cycloalkyloxy groups, C_{7-9} aralkyloxy groups, C_{6-14} aryloxy groups, mercapto group, C_{1-4} alkylthio groups, C_{7-9} aralkylthio groups C_{6-14} arylthio groups, sulfo group, cyano group, azido group, nitro group, nitroso group and halogen atom.

In the formula (I), R is preferably an optionally substituted heterocyclic group. R is more preferably pyridyl, oxazolyl or thiazolyl group which is optionally substituted by 1 to 3 substituents selected from C_{1-3} alkyl group, furyl group, thienyl group, phenyl group and naphthyl group.

R' in the formula (II) has the same definition as R except that R' does not represent benzopyranyl group when m and n are O; X represents CH; A represents a bond; Q represents sulfur atom; R^1, L and M represent hydrogen atom; and ring E does not have further substituents.

In the formulae (I) and (II), Y represents —CO—, —CH(OH)— or —NR^3— (wherein R^3 represents an optionally substituted alkyl group), preferably —CH(OH)— or —NR^3—. As the alkyl group in the optionally substituted alkyl group represented by R^3, mention is made of, for example, C_{1-4} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl and t.-butyl. Examples of the substituents include halogen (e.g., fluorine, chlorine, bromine and iodine), C_{1-4} alkoxy groups (e.g. methoxy, ethoxy, propoxy, butoxy, isobutoxy, sec.-butoxy and t.-butoxy), hydroxyl group, nitro group and C_{1-4} acyl groups (e.g. formyl, acetyl and propionyl).

The symbol m is 0 or 1, preferably 0.

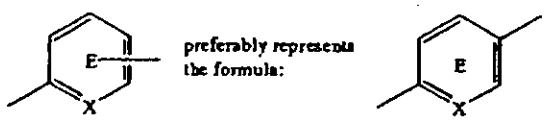
The symbol n is 0, 1 or 2, preferably 0 or 1.

X represents CH or N, preferably CH.

In the formulae (I) and (II), A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group. The aliphatic hydrocarbon group may be straight-chain or branched, and saturated or unsaturated. Specific examples of the aliphatic hydrocarbon group include saturated ones [e.g. —CH_2—, —$CH(CH_3)$—, —$(CH_2)_2$—, —$CH(C_2H_5)$—, —$(CH_2)_3$—, —$(CH_2)_4$—, —$(CH_2)_5$—, —$(CH_2)_6$— and —$(CH_2)_7$—] and unsaturated ones [e.g. —CH=CH—, —$C(CH_3)$=CH—, —CH=CH—CH_2—, —$C(C_2H_5)$=CH—, —CH_2—CH=CH—CH_2—, —CH_2—CH_2—CH=CH—CH_2—, —CH=CH—CH=CH—CH_2— and —CH=CH—CH=CH—CH=CH—CH_2—. A is preferably a bond or C_{1-4} divalent aliphatic hydrocarbon groups, the aliphatic hydrocarbon groups preferably being saturated. A is more preferably a bond or —$(CH_2)_2$—.

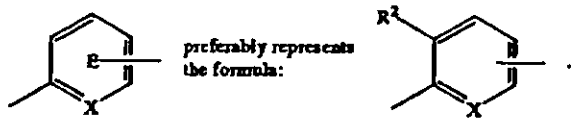
As the alkyl group represented by R^1, substantially the same one as the alkyl group in the above-mentioned R^3. R^1 is preferably hydrogen atom.

In the formulae (I) and (II), the partial formula:



Ring E has 1 to 4 substituents at any substitutable positions. Examples of such substituents include alkyl group, optionally substituted hydroxyl group, halogen atom, optionally substituted acyl group and optionally substituted amino group. These substituents have substantially the same meaning as those described as substituents of the hydrocarbon group and heterocyclic group represented by R.

Ring E, namely the partial formula:



wherein R^2 represents hydrogen atom, an alkyl group, an optionally substituted hydroxyl group, a halogen atom, an optionally substituted acyl group, nitro group or an optionally substituted amino group.

As the alkyl group, optionally substituted hydroxyl group, halogen atom, optionally substituted acyl group and optionally substituted amino group represented by R^2, mention is made of those described as substituents of the hydrocarbon group and heterocyclic group represented by R. R^2 is preferably hydrogen atom, optionally substituted hydroxyl group or halogen atom, more preferably hydrogen atom or optionally substituted hydroxyl group, especially preferably hydrogen atom or C_{1-4} alkoxy groups.

In the formulae (I) and (II), L and M represent hydrogen atom, or they may optionally be combined with each other to form a bond. L and M are preferably hydrogen atom.

In the compounds wherein L and M are combined with each other to form a bond, there exist (E)- and (Z)- isomers relative to the double bond at the 5-position of the azolidinedione ring.

And, in the compounds wherein L and M respectively represent hydrogen atom, there exist (R)- and (S)- optical isomers due to the asymmetric carbon at the 5-position of the azolidinedione ring. The compounds include these (R)- and (S)- optical isomers and racemic isomers.

Preferable examples of the compounds represented by the formula (I) or (II) includes those in which R is pyridyl, oxazolyl or thiazolyl group optionally having 1 to 3 substituents selected from C_{1-3} alkyl, furyl, thienyl, phenyl and naphthyl; m is 0; n is 0 or 1; X is CH; A is a bond or $-(CH_2)_2-$; R^1 is hydrogen atom; ring E, namely the partial formula:

and R^2 is hydrogen atom or C_{1-4} alkoxy group; and L and M are both hydrogen atom.

Preferable examples of the compound represented by the formula (I) include

(1) the compound represented by the formula (III) such as 5-[4-[2-(3-ethyl-2-pyridyl)ethoxy]-benzyl]-2,4-thiazolidinedione; 5-[4-[2-(4-ethyl-2-pyridyl)ethoxy]-benzyl]-2,4-thiazolidinedione; 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (generic name: pioglitazone); and 5-[4-[2-(6-ethyl-2-pyridyl)-ethoxy]benzyl]-2,4-thiazolidinedione;

(2) (R)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione; and

(3) 5-[(4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (generic name: troglitazone/CS-045)

The compound represented by the formula (I) is especially preferably pioglitazone.

The compound represented by the formula (II) is preferably the compound represented by the formula (III) and (R)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione, more preferably pioglitazone.

The pharmacologically acceptable salt of the compound represented by the formula (I) or (II) are exemplified by salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

Preferable examples of salts with inorganic bases include salts with alkali metals such as sodium, potassium, etc., salts with alkaline earth metals such as calcium, magnesium, etc., and salts with aluminum, ammonium, etc.

Preferable examples of salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, etc.

Preferable examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.

Preferable examples of salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acids benzenesulfonic acid, p-toluenesulfonic acid, etc.

Preferable examples of salts with basic amino acids include salts with arginine, lysine, ornithine, etc., and preferable examples of salts with acidic amino acids include salts with aspartic acid, glutamic acid, etc.

The pharmacologically acceptable salt of the compound represented by the formula (III) is preferably a salt with an inorganic acid, more preferably a salt with hydrochloric acid. Especially, pioglitazone is preferably used in the form of salt with hydrochloric acid.

The compounds represented by the formula (I) or (II) or a salt thereof can be produced in accordance with, for example, methods described in JPA S55(1980)-22636(EP-A 8203), JPA S60(1985)-208980(EP-A 155845), JPA S61(1986)-286376(EP-A 208420), JPA S61(1986)-85372(EP-A 177353), JPA S61(1986)-267580(EP-A 193256), JPA H5(1993)-86057(WO 92/18501), JPA H7(1995)-82269 (EP-A 605228), JPA H7(1995)-101945(EP-A 612743), EP-A. 643050, EP-A 710659, etc. or methods analogous thereto.

Insulin sensitivity enhancers include 5-[[3,4-dihydro-2-(phenylmethyl)-2H-1-benzopyran-6-yl]methyl]-2,4-thiazolidinedione (generic name: englitazone) or its sodium salt;

5-[[4-[3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl]phenyl]methyl]-2,4-thiazolidinedione (generic name: darglitazone/CP-86325) or its sodium salt;

5-[2-(5-methyl-2-phenyl-4-oxazolylmethyl)benzofuran-5-ylmethyl]-2,4-oxazolidinedione (CP-92768);

5-(2-naphthalenylsulfonyl)-2,4-thiazolidinedione (AY-31637);

4-[(2-naphthalenyl)methyl]-3H-1,2,3,5-oxathiadiazol-2-oxide (AY-30711); and

5-[[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]-methyl], 2,4-thiazolinedione (BRL-49653), etc. in addition to compounds mentioned hereinbefore.

In the present invention, examples of the drug which is used in combination with the above-mentioned insulin sensitivity enhancer include an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor.

α-Glucosidase inhibitors are drugs which inhibit digestive enzymes such as amylase, maltase, α-dextrinase, sucrase, etc. to retard digestion of starch and sugars. Examples of the α-glucosidase inhibitors, include acarbose, N-(1,3-dihydroxy-2-propyl)valiolamine (generic name; voglibose), miglitol, etc. with preferance given to voglibose.

Aldose reductase inhibitors are drugs which inhibit the first-stage rate-limitting enzyme in the polyol pathway to prevent or arrest diabetic complications. In the hyperglycemic state of diabetes, the utilization of glucose in the polyol pathway is increased and the excess sorbitol accumulated intracellularly as a consequence acts as a tissue toxin and hence evokes the onset of complications such as diabetic neuropathy, retinopathy, and nephropathy. Examples of the aldose reductase inhibitors include tolurestat; epalrestat; 3,4-dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxazine-4-acetic acid; 2,7-difluoro-spiro(9H-fluorene-9,4'-imidazolidine)-2 ', 5'-dione (generic name: imirestat);

3-[(4-bromo-2-fluorophenyl)methyl]-7-chloro-3,4-dihydro-2,4-dioxo-1(2H)-quinazoline acetic acid (generic name: zenarestat);

6-fluoro-2,3-dihydro-2', 5'-dioxo-spiro[4H-1-benzopyran-4,4'-imidazolidine]-2-carboxamide (SNK-860);

zopolrestat; sorbinil; and

1-[(3-bromo-2-benzofuranyl)sulfonyl]-2,4-imidazolidinedione (M-16209), etc.

Biguanides are drugs having actions of stimulation of anaerobic glycolysis, increase of the sensitivity to insulin in the peripheral tissues, inhibition of glucose absorption from the intestine, suppression of hepatic gluconeogenesis, and inhibition of fatty acid oxidation. Examples of the biguanides include phenformin, metformin, buformin etc.

Statin compounds are drugs having actions of lowering blood cholesterol levels by inhibiting hydroxymethylglutalyl CoA (HMG-CoA) reductase. Examples of the statin compounds include pravastatin and its sodium salt, simvastatin, lovastatin, atorvastatin, fluvastatin, etc.

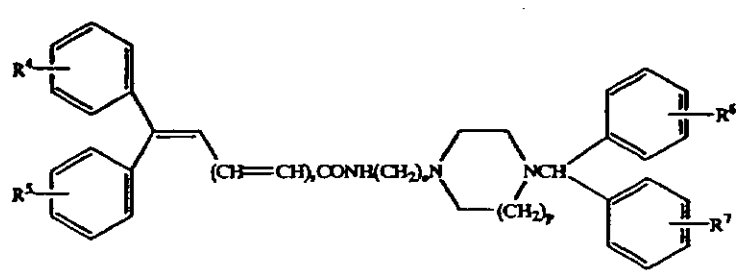
Squalene synthesis inhibitors are drugs having actions of lowering blood cholesterol levels by inhibiting synthesis of squalene. Examples of the squalene synthesis inhibitors include (S)-α-[Bis[2,2-dimethyl-1-oxopropoxy)methoxy] phosphinyl]-3-phenoxybenzenebutanesulfonic acid, mono potassium salt (BMS-188494).

Fibrate compounds are drugs having actions of lowering blood cholesterol levels by inhibiting synthesis and secretion of triglycerides in liver and activating a lipoprotein lipase.

Examples of the fibrate compounds include bezafibrate, beclobrate, binifibrate, ciprofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate, etc.

LDL catabolism enhancers are drugs having actions of lowering blood cholesterol levels by increasing the number of LDL (low-density lipoprotein) receptors.

Examples of the LDL catabolism enhancers include the compound which is described in JPA H7(1995)-316144and represented by the formula:



wherein R^4, R^5, R^6 and R^7 are the same or different, and represent hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group; r is 0–2; s is 2–4; p is 1–2; or a salt thereof; specifically N-[2-[4-bis(4-fluorophenyl) methyl-1-piperazinyl]ethyl]-7,7-diphenyl-2,4,6-heptatrienic acid amide, etc.

The above-mentioned statin compounds, squalene synthesis inhibitors, fibrate compounds and LDL catabolism enhancers can be substituted with other drugs having the property to lower blood cholesterol and triglyceride levels. Examples of these drugs include nicotinic acid derivatives such as nicomol and niceritrol; antioxidants such as probucol; and ion-exchange resins such as colestyramin.

Angiotensin converting enzyme inhibitors are drugs having actions of partially lowering blood glucose levels as well as lowering blood pressure by inhibiting angiotensin converting enzymes. Examples of the angiotensin converting enzyme inhibitors include captopril, enalapril, alacepril, delapril, ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moveltopril, perindopril, quinapril, spirapril, temocapril, trandolapril, etc.

In the present invention, especially preferred is the pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with an α-glucosidase inhibitor. The insulin sensitivity enhancer is especially preferably pioglitazone, and the α-glucosidase inhibitor is especially preferably voglibose.

In the present invention, examples of the drug which is used in combination with the compound represented by the formula (II) or a pharmacologically acceptable salt thereof include an insulin secretion enhancer and/or an insulin preparation.

Insulin secretion enhancers are drugs having the property to promote secretion of insulin from pancreatic β cells.

Examples of the insulin secretion enhancers include sulfonylureas (SU). The sulfonylureas (SU) are drugs which promote secretion of insulin from pancreatic β cells by transmitting signals of insulin secretion via SU receptors in the cell membranes. Examples of the SU include tolbutamide; chlorpropamide; tolazamide; acetohexamide; 4-chloro-N-[(1-pyrolidinylamino)carbonyl]-benzenesulfonamide (generic name: glycopyramide) or its ammonium salt; glibenclamide (glyburide); gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; tolcyclamide, etc.

Insulin secretion enhancers include N-[[4-(1-methylethyl) cyclohexyl]carbonyl]-D-phenylalanine (AY-4166); calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl) propionate dihydrate (KAD-1229); and glimepiride (Hoe 490), etc. in addition to compounds mentioned hereinbefore. The insulin secretion enhancer is especially preferably glibenclamide.

Examples of the insulin preparations include animal insulin preparations typically extracted from bovine or porcine pancreas and human insulin preparations synthesized by genetic engineering techniques typically using *Escherichia coli* or yeasts. While insulin preparations are available in a variety of types, e.g. immediate-acting, bimodal-acting, intermediate-acting, and long-acting, these types of preparations can be selectively administered according to the patient's condition.

In the present invention, especially preferred is the pharmaceutical composition which comprises the compound represented by the formula (II) or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer. The compound represented by the formula (II) or a pharmacologically acceptable salt thereof is especially preferably pioglitazone, and the insulin secretion enhancer is especially preferably glibenclamide.

The pharmaceutical composition comprising an insulin sensitivity enhancer in combination with at least one member selected from the group consisting of an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor; and the pharmaceutical composition comprising the compound represented by the formula (II) or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation, both provided in accordance with the present invention, can be respectively put to use by mixing the respective active components either all together or independently with a physiologically acceptable carrier, excipient, binder, diluent, etc. and administering the mixture or mixtures either orally or non-orally as a pharmaceutical composition. When the active components are formulated independently, the respective formulations can be extemporaneously admixed using a diluent or the like and administered or can be administered independently of each other, either concurrently or at staggered times to the same subject.

The dosage form for said pharmaceutical composition includes such oral dosage forms as granules, powders, tablets, capsules, syrups, emulsions, suspensions, etc. and such non-oral dosage forms as injections (e.g. subcutaneous, intravenous, intramuscular and intraperitoneal injections), drip infusions, external application forms (e.g. nasal spray preparations, transdermal preparations, ointments, etc.), and suppositories (e.g. rectal and vaginal suppositories).

These dosage forms can be manufactured by the per se known technique conventionally used in pharmaceutical procedures. The specific manufacturing procedures are as follows.

To manufacture an oral dosage form, an excipient (e.g. lactose, sucrose, starch, mannitol, etc.), a disintegrator (e.g. calcium carbonate, carboxymethylcellulose calcium, etc.), a binder (e.g. α-starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, etc.), and a lubricant (e.g. talc, magnesium stearate, polyethylene glycol 6000, etc.), for instance, are added to the active component or components and the resulting composition is compressed. Where necessary, the compressed product is coated, by the per se known technique, for masking the taste or for enteric dissolution or sustained release. The coating material that can be used includes, for instance, ethyl-cellulose, hydroxymethylcellulose, polyoxyethylene glycol, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, and Eudragit (Rohm & Haas, Germany, methacrylic-acrylic copolymer).

Injections can be manufactured typically by the following procedure. The active component or components are dissolved, suspended or emulsified in an aqueous vehicle (e.g. distilled water, physiological saline, Ringer's solution, etc.) or an oily vehicle (e.g. vegitable oil such as olive oil, sesame oil, cottonseed oil, corn oil, etc. or propylene glycol) together with a dispersant (e.g. Tween 80 (Atlas Powder, U.S.A.), HCO 60 (Nikko Chemicals), polyethylene glycol, carboxymethylcellulose, sodium alginate, etc.), a preservative (e.g. methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, benzyl alcohol, chlorobutanol, phenol, etc.), an isotonizing agent (e.g. sodium chloride, glycerol, sorbitol, glucose, inverted sugar, etc.) and other additives. If desired, a solubilizer (e.g. sodium salicylate, sodium acetate, etc.), a stabilizer (e.g. human serum albumin), a soothing agent (e.g. benzalkonium chloride, procaine hydrochloride, etc.) and other additives can also be added.

A dosage form for external application can be manufactured by processing the active component or components into a solid, semi-solid or liquid composition. To manufacture a solid composition, for instance, the active component or components, either as they are or in admixture with an excipient (e.g. lactose, mannitol, starch, microcrystalline cellulose, sucrose, etc.), a thickener (e.g. natural gums, cellulose derivatives, acrylic polymers, etc.), etc., are processed into powders. The liquid composition can be manufactured in substantially the same manner as the injections mentioned above. The semi-solid composition is preferably provided in a hydrous or oily gel form or an ointment form. These compositions may optionally contain a pH control agent (e.g. carbonic acid, phosphoric acid, citric acid, hydrochloric acid, sodium hydroxide, etc.), and a preservative (e.g. p-hydroxybenzoic acid esters, chlorobutanol, benzalkonium chloride, etc.), among other additives.

Suppositories can be manufactured by processing the active component or components into an oily or aqueous composition, whether solid, semi-solid or liquid. The oleaginous base that can be used includes, for instance, higher fatty acid glycerides [e.g. cacao butter, Witepsols (Dinamit-Nobel), etc.], medium-chain fatty acids [e.g. Migriols (Dinamit-Nobel), etc.], vegetable oils (e.g. sesame oil, soybean oil, cottonseed oil, etc.), etc. The water-soluble base includes, for instance, polyethylene glycols, propylene glycol, etc. The hydrophilic base includes, for instance, natural gums, cellulose derivatives, vinyl polymers, and acrylic polymers, etc.

The pharmaceutical composition of the present invention is low in toxicity and can be safely used in mammals (e.g. humans, mice, rats, rabbits, dogs, cats, bovines, horses, swines, monkeys).

The dosage of the pharmaceutical composition of the present invention may be appropriately determined with

reference to the dosages recommended for the respective active components and can be selected appropriately according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of the active components, among other factors. For example, the dosage of the insulin sensitivity enhancer for an adult can be selected from the clinical oral dose range of 0.01 to 10 mg/kg body weight (preferably 0.05 to 10 mg/kg boday weight, more preferably 0.05 to 5 mg/kg body weight) or the clinical parenteral dose range of 0.005 to 10 mg/kg body weight (preferably 0.01 to 10 mg/kg body weight, more preferably 0.01 to 1 mg/kg body, weight). The other active component or components having different modes of action for use in combination can also be used in dose ranges selected by referring to the respective recommended clinical dose ranges. The preferred frequency of administration is 1 to 3 times a day.

The proportions of the active components in the pharmaceutical composition of the present invention can be appropriately selected according to the recipient, the recipient's age and body weight, current clinical status, administration time, dosage form, method of administration, and combination of active components, among other factors. When, for example, the compound represented by the formula (I) or a pharmacologically acceptable salt thereof (e.g. pioglilazone) which is the insulin sensitivity enhancer and voglibose which is an α-glucosidase inhibitor are to be administered in combination to a human subject, voglibose is used in a proportion of usually about 0.0001 to 0.2 weight parts and preferably about 0.001 to 0.02 weight parts relative to 1 weight part of the compound or a salt thereof. When, for example, the compound represented by the formula (II) or a pharmacologically acceptable salt thereof and glibenclamide which is an insulin secretion enhancer are to be administered in combination to a human subject, glibenclamide is used in a proportion of usually about 0.002 to 5 weight parts and preferably about 0.025 to 0.5 weight parts, relative to 1 weight-part of the compound or a pharmacologically acceptable salt thereof.

The pharmaceutical composition of the present invention shows a marked synergistic effect compared with administration of either active component alone. For example, compared with cases in which each of these active components was administered to diabetic Wistar fatty rats with genetical obsesity, administration of these active components in combination resulted in marked improvements in both hyperglycemia and reduced glucose tolerance. Thus, the pharmaceutical composition of the present invention lowers blood glucose in diabetics more effectively than it is the case with administration of each component drug alone and, therefore, can be used advantageously for the prophylaxis and treatment of diabetic complications.

Furthermore, since the pharmaceutical composition of the present invention develops sufficient efficacy with reduced doses as compared with the administration of any one of the active components alone, the side effects of the respective components (e.g. gastrointestinal disorders such as diarrhea, etc.) can be reduced.

The following working examples and experimental examples are merely intended to illustrate the present invention in further detail but should by no means be construed as defining the scope of the-invention.

The pharmaceutical composition of the present invention can be prepared according to the following formulations.

WORKING EXAMPLE 1

Capsules	
(1) Pioglitazone hydrochloride	30 mg
(2) Voglibose	0.2 mg
(3) Lactose	60 mg
(4) Microcrystalline cellulose	79.8 mg
(5) Magnesium stearate	10 mg
Total	180 mg

The whole amounts of (1), (2), (3) and (4) and half the amount of (5) are mixed well and granulated in the conventional manner. Then, the balance of (5) is added and, after mixing, the whole composition is filled in a gelatin hard capsule shell.

WORKING EXAMPLE 2

Tablets	
(1) Pioglitazone hydrochloride	10 mg
(2) Glibenclamide	1.25 mg
(3) Lactose	86.25 mg
(4) Corn starch	20 mg
(5) Polyethylene glycol	2.5 mg
(6) Hydroxypropylcellulose	4 mg
(7) Carmellose calcium	5.5 mg
(8) Magnesium stearate	0.5 mg
	130 mg (per tablet)

The whole amounts of (1), (2), (3), (4), and (5), ⅔ amounts of (6) and (7), and ½ amount of (8) are mixed well and granulated in the conventional manner. Then, the balances of (6), (7) and (8) are added to the granules, which is mixed well and the whole composition is compressed with a tablet machine. The adult dosage is 3 tablets/day, to be taken in 1 to 3 divided doses.

WORKING EXAMPLE 3

Capsules	
(1) Pioglitazone hydrochloride	30 mg
(2) Epalrestat	50 mg
(3) Lactose	55 mg
(4) Microcrystalline cellulose	55 mg
(5) Magnesium stearate	10 mg
Total	180 mg

The whole amounts of (1), (2), (3) and (4) and ½ amount of (5) are mixed well and granulated in the conventional manner. Then, the balance of (5) is added and the whole composition is filled in gelatin capsule shell. The adult dosage is 3 capsules/day, to be taken in 1 to 3 divided doses.

Experimental Example 1

Effect of pioglitazone hydrochloride in combination with α-glucosidase inhibitor in genetically obese and diabetic Wistar fatty rats.

Male Wistar fatty rats aged 14–19 weeks were divided into 4 groups of 5–6, and pioglitazone hydrochloride (1 mg/kg body wt./day, p.o.) and/or voglibose (an α-glucosidase inhibitor) (0.31 mg/)kg body wt./day; administered by mixing in commercial diet at a rate of 5 ppm) was

administered for 14 days. The blood was then collected from the tail vein and the plasma glucose and hemoglobin A_1 were determined by the enzymatic method (Encore Chemical System, Baker) and using a commercial kit (NC-ROPET, Nippon Chemiphar Co.), respectively. The results were expressed in mean ± standard deviation for each group (n=5–6) and analyzed by Dunnett's test, which are shown in Table 1.

The 1% level of significance was used.

TABLE 1

Group	Plasma glucose (mg/dl)	Hemoglobin A_1 (%)
Control	345 ± 29	5.7 ± 0.4
Pioglitazone	215 ± 50*	5.2 ± 0.3
Voglibose	326 ± 46	6.0 ± 0.6
Pioglitazone + voglibose	114 ± 23*	4.5 ± 0.4*

*P < 0.01 vs. control group

It is apparent from Table 1 that both the blood glucose and hemoglobin A_1 levels were remarkably lowered by combined administration of pioglitazone and voglibose as compared with the administration of either drug alone.

Experimental Example 2

Effect of pioglitazone hydrochloride in combination with an insulin secretion enhancer in genetically obese and diabetic Wistar fatty rats.

Male Wistar fatty rats aged 13–14 weeks were divided into 4 groups of 5, and pioglitazone hydrochloride (3 mg/kg/day, p.o.) and/or glibenclamide (an insulin secretion enhancer) (3 mg/kg/day, p.o.) was administered for 7 days. Following an overnight fast, the oral glucose loading test (2 g glucose/kg/5 ml, p.o.) was carried out. Prior to glucose loading and 120 and 240 minutes after the loading, blood was collected from the tail vein and the plasma glucose was assayed by the enzymatic method (Encore Chemical System, Baker). The results were expressed in mean ± SD for each group (n=5) and analyzed by Dunnett's test, which are shown in Table 2.

TABLE 2

Group	Plasma glucose (mg/dl) 0 min.	120 min.	240 min.
Control	119 ± 9	241 ± 58	137 ± 10
Pioglitazone	102 ± 12	136 ± 17*	102 ± 9*
Glibenclamide	118 ± 12	222 ± 61	106 ± 24*
Pioglitazone + glibenclamide	108 ± 3	86 ± 10*	60 ± 5*

*P < 0.01 vs. control group

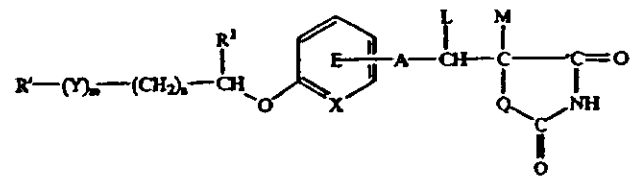
It is apparent from Table 2 that the increase of blood sugar following glucose loading was remarkably inhibited by the combined administration of pioglitazone and glibenclamide as compared with the administration of either drug alone.

The pharmaceutical composition of the present invention shows a potent depressive effect on diabetic hyperglycemia and is useful for prophylaxis and treatment of diabetes. Moreover, this pharmaceutical composition is useful for prophylaxis and treatment of diabetic complications such as diabetic neuropathy, nephropathy, retinopathy, macroangiopathy, and osteopenia. In addition, by appropriately selecting the kinds of component drugs, administration route, dosage, etc. according to clinical status, stable. hypoglycemic efficacy in long-term therapy can be expected with an extremely low risk of side effect.

What is claimed is:

1. A method for reducing the side effects of respective active components administered to a diabetic patient, which comprises administering to said patient a therapeutically effective amount of a compound represented by the formula:

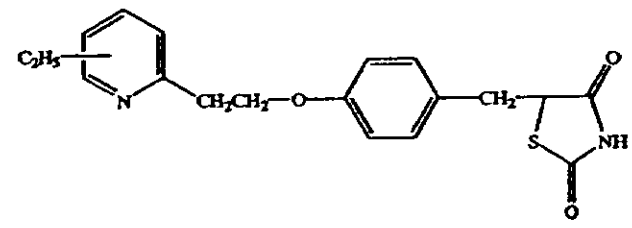
(II)



wherein R' represents an optionally substituted hydrocarbon or heterocyclic group; Y represents a group represented by —CO—, —CH(OH)— or —NR^3— wherein R^3 represents an optionally substituted alkyl group; m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a bond or a C_{1-7} divalent aliphatic hydrocarbon group; Q represents an oxygen atom or sulfur atom; R^2 represents hydrogen atom or an alkyl group; ring E may optionally have 1 to 4 further substituents, and the substituents may optionally be combined with R^2 to form a ring; L and M respectively represent a hydrogen atom, or L and M may optionally be combined with each other to form a bond; with a proviso that R' does not represent benzopyranyl group when m and n are 0, X represents CH, A represents a bond, Q represents sulfur atom, R^1, L and M represent hydrogen atoms and ring E does not have further substituents; or a pharmacologically acceptable salt thereof, in combination with an insulin secretion enhancer.

2. The method according to claim 1, wherein the compound represented by the formula (II) is the compound represented by the formula:

(III)



3. The method according to claim 1, wherein the compound represented by the formula (II) is pioglitazone or its pharmacologically acceptable salts.

4. The method according to claim 1, wherein the insulin secretion enhancer is glibenclamide.

5. The method according to claim 1, wherein the compound represented by the formula (II) is pioglitazone and the insulin secretion enhancer is glibenclamide.

6. The method according to claim 1, wherein the compound represented by the formula (II) is 5-[[4-[2(-methyl-2-pyridylamino)ethoxy]phenyl]methyl-2,4-thiazolidinedione or its pharmacologically acceptable salts.

7. The method according to claim 1, wherein the compound represented by the formula (II) is troglitazone or its pharmacologically acceptable salts.

8. The method according to claim 1, wherein the insulin secretion enhancer is a sulfonylurea.

9. The method according to claim 8, wherein the sulfonylurea is selected from tolbutamide, chlorpropamide,

tolazamide, acetohexamide, 4chloro-N-[(1-pyrolidinylamino)carbonyl]-benzenesulfonamide or its ammonium salt, glibenclamide, gliclazide, 1-butyl-3-metanilylurea, carbutamide, glibonuride, glipizide, gliquidone, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide and tolcyclamide.

10. The method according to claim 1, wherein R' is an optionally substituted heterocyclic group.

11. The method according to claim 10, wherein R' is selected from the group consisting of 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4thiazolyl, 5-thiazolyl, 2-oxazolyl, 4oxazolyl, 5-oxazolyl, 1,2,4oxadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, 1H-indazol-3-yl, 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 1H-imidazo[4,5-b]pyrazin-2-yl and benzopyranyl; each of which may have 1 to 5 substituents selected from the group consisting of C_{1-15} aliphatic hydrocarbon group; C_{3-12} alicyclic hydrocarbon group; C_{6-14} aryl group; aromatic heterocyclic group selected form the group consisting of furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4,-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4thiadiazolyl, 1,3,4thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, 1,2-benzoisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylidinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, βcarbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenathridinyl, phenathrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1, 2,4triazolo[4, 3-a]pyridyl and 1,2,4triazolo[4,3-b]pyridazinyl; non-aromatic heterocyclic group selected from the group consisting of oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidino, piperidino, morpholino and thiomorpholino; halogen atom; nitro group; amino groups which may have one or two substituents selected from C_{1-10} alkyl group, C_{2-10} alkenyl group, C_{2-10} alkynyl group, aromatic group, heterocyclic group or C_{1-10} acyl group; C_{1-13} acyl group which may be substituted by C_{1-3} alkyl group, C_{1-3} alkoxy group, halogen atom, nitro group, hydroxyl group or amino group; hydroxyl group; C_{1-10} alkoxy group; C_{3-10} cycloalkyloxy group; C_{2-10} alkenyloxy group; C_{3-10} cycloalkenyloxy group; C_{7-10} aralkyloxy group; C_{2-13} acyloxy group; C_{6-14} aryloxy group which may be substituted with one or two halogen atoms; thiol group; C_{1-10} alkylthio group; C_{3-10} cycloalkylthio group; C_{2-10} alkenylthio group; C_{3-10} cycloalkenylthio group, C_{7-10} aralkylthio group, C_{2-13} acylthio group; C_{6-14} arylthio group which may be substituted with one or two halogen atoms; carboxyl group; C_{2-5} alkoxycarbonyl group; C_{8-10} aralkyloxycarbonyl group; C_{7-15} aryloxycarbonyl group; amidino group; carbamoyl group; sulfamoyl group; sulfo group; cyano group; azido group and nitroso group.

12. The method according to claim 1, wherein the insulin secretion enhancer is selected from the group consisting of N-[[4-(1-methylethyl)cyclohexyl)carbonyl]-D-phenylalanine; calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl) propionate dihydrate and glimepiride.

* * * * *

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September 9, 2003

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Re: Pioglitazone Hydrochloride Tablets (15 mg, 30 mg and 45 mg)

Dear Mr. Shinha and Ms. Dubas:

We are writing on behalf of Watson Pharmaceuticals, Inc. ("Watson"), pursuant to 21 U.S.C. § 355(j)(2)(B)(ii), to inform you that, in order to obtain approval to engage in the commercial manufacture, use or sale of pioglitazone hydrochloride ("pioglitazone HCl") tablets (15 mg, 30 mg and 45 mg), Watson submitted to the United States Food and Drug Administration ("FDA") an Abbreviated New Drug Application ("ANDA") under 21 U.S.C. § 355(j)(1) and (2)(A), which contains data from bioavailability or bioequivalence studies. This application has been assigned ANDA number 76-798 ("the Application").

The Application, which includes a Paragraph IV certification, indicates that Watson intends to market its pioglitazone HCl tablets before the expiration of U.S. Patents 5,965,584 ("the '584 patent") and 6,329,404 ("the '404 patent"). The Application further certifies that in Watson's opinion and to the best of its knowledge, the '584 and '404 patents will not be infringed. As required by 21 U.S.C. § 355(j)(2)(B)(ii), a detailed statement of the factual and legal basis upon which Watson bases its opinion is set forth below.

Claims 1-5, 11 and 15 of the '584 patent relate to a pharmaceutical composition comprising an insulin sensitivity enhancer (e.g., pioglitazone) in combination with a biguanide (e.g., metformin). For purposes of Watson's Paragraph IV certification, only these claims of the '584 patent are relevant. The remaining claims 6-10, 12-14 and 16 are directed to an indication (i.e., the combination therapy of an insulin sensitivity enhancer and a biguanide) for which Watson does not seek approval. Accordingly, no Paragraph IV certification with respect to claims 6-10, 12-14 and 16 of the '584 patent is required.

Claims 1-12 of the '404 patent are directed to a pharmaceutical composition comprising an insulin sensitivity enhancer (e.g., pioglitazone) in combination with an insulin secretion enhancer (e.g., a sulfonylurea). For purposes of Watson's Paragraph IV certification, only these claims of the '404 patent are relevant. The remaining claims 13-25 are directed to an indication (i.e., the combination therapy of an insulin sensitivity enhancer and an insulin secretion enhancer) for which Watson does not seek approval. Accordingly, no Paragraph IV certification with respect to claims 13-25 of the '404 patent is required.

Watson's pioglitazone HCl tables (15 mg, 30 mg and 45 mg) contain only one active ingredient, namely pioglitazone HCl. Moreover, no active ingredient, other than pioglitazone HCl, is introduced at any time in the manufacture of Watson's pioglitazone HCl tablets. Further, the proposed labeling confirms that pioglitazone HCl is the only active agent contained in Watson's pioglitazone HCl tablets (15 mg, 30 mg and 45 mg).

In addition, Watson's labeling references the use of pioglitazone HCl tablets (15 mg, 30 mg and 45 mg) for monotherapy as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. The package insert label for Watson's pioglitazone HCl label does not provide for any indication of pioglitazone HCl in combination with a sulfonylurea, metformin or insulin (or any other active agent). Moreover, the dosage and administration information on Watson's label recites only monotherapy for pioglitazone HCl tablets and not combination therapy with any other active ingredient, such as a sulfonylurea, metformin, or insulin.

Generally, there are two ways a claim can be directly infringed. A claim can be either (a) literally infringed or (b) infringed under what is known as the "doctrine of equivalents." If the accused product has *every* element of a claim, literal infringement is established.

Lemelson v. United States, 752 F.2d 1538, 1551 (Fed. Cir. 1985); *Pennwalt Corp. v. Durand-Wayland, Inc.*, 833 F.2d 931 (Fed. Cir. 1987) (*en banc*), *cert. denied*, 485 U.S. 961 (1988). All claim elements are material and must be present to find infringement. *Hubbell v. United States*, 179 U.S. 77, 82 (1900). ("[A]ll [specified elements] must be regarded as material"). This is sometimes referred to as the "all elements" rule.

If there is not a literal correspondence between the elements of a claim and the accused product, there may still be infringement under the doctrine of equivalents if the accused product contains the substantial equivalent of each and every one of the elements of the asserted claim. *Graver Tank & Mfg. Co. v. Linde Air Products Co.*, 339 U.S. 605, 607-08 (1950); *Hughes Aircraft Co. v. United States*, 717 F.2d 1351, 1361 (Fed. Cir. 1983); *Pennwalt Corp.*, 833 F.2d 931; *Malta v. Schulmerich Carillons, Inc.*, 952 F.2d 1320, 1325 (Fed. Cir. 1991), *cert. denied*, 112 S.Ct. 2942 (1992). This doctrine comes into play only when literal infringement is not present. Under the doctrine, an accused product that does not literally infringe a claim may be found to infringe if it performs substantially the same function in substantially the same way to obtain the same or substantially the same result as the claimed invention. *Graver Tank*, 329 U.S. at 607-08.

From the foregoing, it is clear that Watson's pioglitazone HCl tablets (15 mg, 30 mg and 45 mg) do not infringe claims 1-5, 11 and 15 of the '584 patent and claims 1-12 of the '404 patent because no second active pharmaceutical ingredient is present in the Watson pioglitazone HCl tablets. Watson's tablets do not include a biguanide, a sulfonylurea or any other active agent. Infringement of a claim based on the aforementioned case law requires that the accused product contain all of the elements of the asserted claim, either literally or through an equivalent thereof. As Watson's pioglitazone HCl tablets (15 mg, 30 mg and 45 mg) contain no biguanide or sulfonylurea, and indeed contains no active agent other than pioglitazone HCl, there is no infringement of the combination product claims of either the '584 or 404 patents.

In conclusion, as indicated above, there is no reasonable basis upon which Takeda Chemical Industries, Ltd. or Takeda Pharmaceuticals America, Inc. can institute suit against Watson for the filing of the Application as the information herein provided to you makes clear. Under these conditions, we would view the filing of litigation against Watson to be a clear violation of Rule 11 of the Federal Rules of Civil Procedure and render the case exceptional under 35 U.S.C. § 285 warranting the award of attorneys' fees to Watson.

Finally, please be advised that Watson intends to obtain final approval of its ANDA and proceed to market its pioglitazone HCl tablets (15 mg, 30 mg and 45 mg) as soon as permitted by applicable statutes and regulations.

If you have any questions after reviewing this letter, please feel free to contact us to discuss this matter further.

Very truly yours,

LEYDIG, VOIT & MAYER, LTD.

Steven H. Sklar